INVENTOR SEARCH

=> fil capl; d que nos l41
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FILE LAST UPDATED: 3 Dec 2007 (20071203/ED)

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| | | |
|---|---|---|
| L1 | | STR |
| L3 | 1 | SEA FILE=CAPLUS ABB=ON US2006-524343/AP |
| L6 | 43 | SEA FILE=REGISTRY SSS FUL L1 |
| L7 | 66323 | SEA FILE=REGISTRY ABB=ON Y[SMLQATN]G[FW]/SQSP |
| L8 | 20680 | SEA FILE=REGISTRY ABB=ON MULTICHAIN/NTE |
| L9 | 283 | SEA FILE=REGISTRY ABB=ON L7 AND L8 |
| L10 | 14340 | SEA FILE=REGISTRY ABB=ON COVALENT/NTE |
| L11 | 236 | SEA FILE=REGISTRY ABB=ON L9 AND L10 |
| L12 | 145 | SEA FILE=REGISTRY ABB=ON L11 AND 8/SQL |
| L13 | 734823 | SEA FILE=REGISTRY ABB=ON HYDRAZIDE |
| L14 | 90 | SEA FILE=REGISTRY ABB=ON L12 AND L13 |
| L26 | 57 | SEA FILE=REGISTRY ABB=ON L14 NOT (NORLEU? OR TRICYCLO? OR LYS?) |
| L27 | 16 | SEA FILE=REGISTRY ABB=ON L26 NOT L6 |
| L30 | 11 | SEA FILE=CAPLUS ABB=ON L27 |
| L32 | 199 | SEA FILE=CAPLUS ABB=ON LIPKOWSKI A?/AU |
| L33 | 895 | SEA FILE=CAPLUS ABB=ON CARR D?/AU |
| L34 | 11 | SEA FILE=CAPLUS ABB=ON BONNEY I?/AU |
| L35 | 127 | SEA FILE=CAPLUS ABB=ON KOSSON D?/AU |
| L36 | 4 | SEA FILE=CAPLUS ABB=ON MISJECKA KESIK A?/AU OR MISJECKA A?/AU OR KESIK A?/AU |
| L37 | 2 | SEA FILE=CAPLUS ABB=ON MISIECKA-KESIK A?/AU OR MISIECKA A?/AU |
| L41 | 7 | SEA FILE=CAPLUS ABB=ON (L3 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37) AND L30 |

=> d ibib abs hitseq l41 1-7

L41 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:200898 CAPLUS Full-text





DOCUMENT NUMBER: 128:283059
TITLE: Modifications of the 4,4'-residues and SAR studies of biphalin, a highly potent opioid receptor active peptide
AUTHOR(S): Li, Guigen; Haq, W.; Xiang, Li; Lou, Bih-Show; Hughes, Robert; De Leon, Irene A.; Davis, Peg; Gillespie, Terrence J.; Romanowski, Marek; Zhu, Xiaoyun; Misicka, Aleksandra; Lipkowski, Andrzej W.; Porreca, Frank; Davis, Thomas P.; Yamamura, Henry I.; O'brien, David F.; Hruby, Victor J.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(5), 555-560
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Modifications of 4,4' residues of biphalin have resulted in greater binding selectivity and biol. potency for the μ opioid receptor. A higher partition coefficient across the phospholipid bilayer membrane has been achieved by using β-branched unusual amino acids.

IT 205759-12-2P 205759-16-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of biphalin analogs and opioid receptor activities)

RN 205759-12-2 CAPLUS

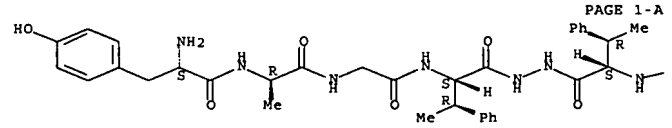
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-β-methyl-, 2-[L-tyrosyl-D-alanylglycyl-(βR)-β-methyl-L-phenylalanyl]hydrazide, (βR)- (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.



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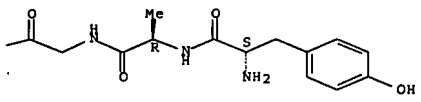


RN 205759-16-6 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-2,3,4,5,6-pentafluoro-, 2-(L-tyrosyl-D-alanylglycyl-2,3,4,5,6-pentafluoro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

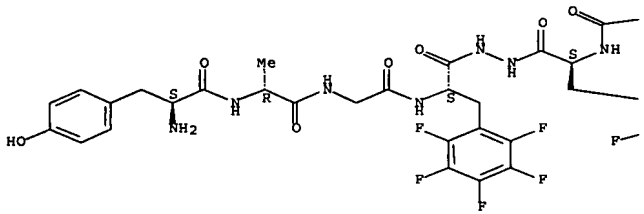
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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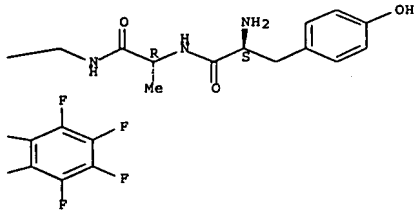






REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:601250 CAPLUS Full-text
DOCUMENT NUMBER: 127:288285
TITLE: Interaction of a highly potent dimeric enkephalin analog, biphalin, with model membranes
AUTHOR(S): Romanowski, Marek; Zhu, Xiaoyun; Ramaswami, Varadarajan; Misicka, Aleksandra; Lipkowski, Andrzej W.; Hruby, Victor J.; O'Brien, David F.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, P.O. Box 210041, Tucson, AZ, USA
SOURCE: Biochimica et Biophysica Acta, Biomembranes (1997), 1329(2), 245-258
CODEN: BBBMBS; ISSN: 0005-2736
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Biphalin, (Tyr-D-Ala-Gly-Phe-NH)2, is a highly potent dimeric analog of enkephalin. Its analgesic efficacy is due in part to its ability to permeate the blood-brain barrier. To aid in understanding the mechanism of the transmembrane movement we determined and analyzed the permeability and partition coeffs. of biphalin and a series of analogs where F, Cl, I, NO2, or NH2 were placed in the para position of the aromatic rings of Phe4,4'. Liposomes composed of neutral phospholipids and cholesterol were used as the model membrane. The overall good correlation between permeability and water-membrane partition coeffs. suggests that the movement of biphalins across the model membrane is controlled by diffusion and depends on the water-membrane partition coefficient To explain the observed correlation between permeability and the electron withdrawing/donating character of the substituents in the phenylalanine ring, we examined various folding patterns of Leu-enkephalin, an endogenous pentapeptide that exhibits affinities toward the same classes of opioid receptors (δ and μ). The observed permeabilities and partition coeffs. of biphalin and analogs, as well as the tyrosine side chain accessibility, are consistent with the presence of the type of folding where the tyrosine and phenylalanine side chains are in a close contact. We propose that the aromatic ring interaction can promote the peptide permeability by stabilizing a more compact structure of biphalin that would minimize the number of hydrogen bonds with water and therefore enhances partitioning into the model membrane.

IT 151608-19-4 155482-41-0 155482-42-1
155482-43-2 189169-89-9
RL: BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); PROC (Process)
(biphalin interaction with model membranes and structure in relation to permeation thereof)

RN 151608-19-4 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-chloro-, 2-(L-tyrosyl-D-alanylglycyl-4-chloro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

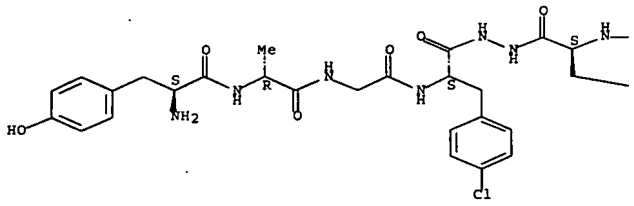
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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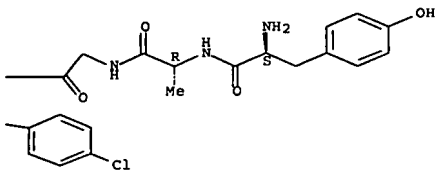


RN 155482-41-0 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-iodo-, 2-(L-tyrosyl-D-alanylglycyl-4-iodo-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified

SEQ 1 YAGF

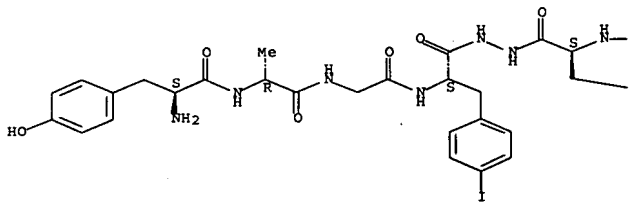
1 YAGF

Absolute stereochemistry.





PAGE 1-A



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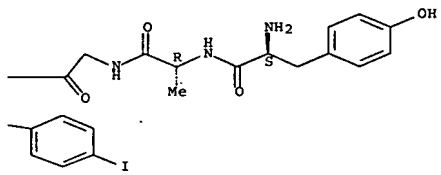


RN 155482-42-1 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-amino-, 2-(L-tyrosyl-D-alanylglycyl-4-amino-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

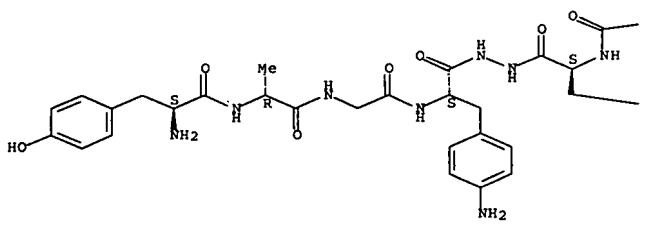
NTE multichain
modified

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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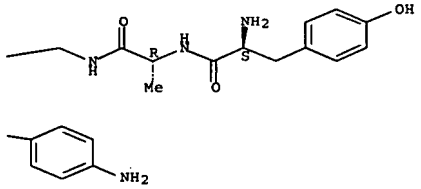


RN 155482-43-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-nitro-, 2-(L-tyrosyl-D-alanylglycyl-4-nitro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified

SEQ 1 YAGF

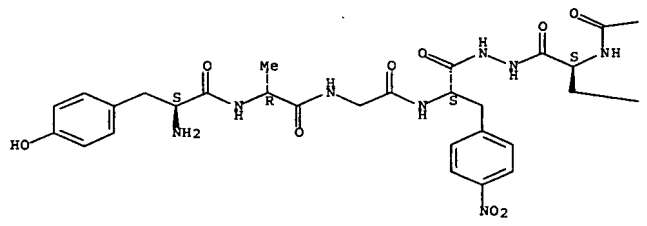
1 YAGF

Absolute stereochemistry.





PAGE 1-A



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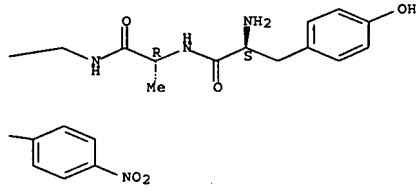


RN 189169-89-9 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-fluoro-, 2-(L-tyrosyl-D-alanylglycyl-4-fluoro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

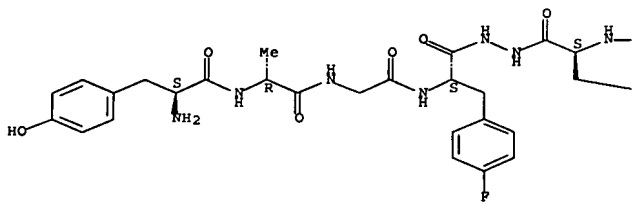
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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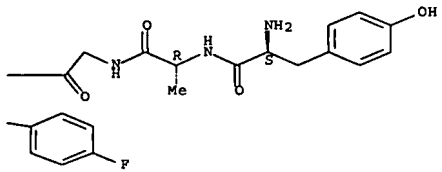


REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:208033 CAPLUS Full-text
DOCUMENT NUMBER: 126:293605
TITLE: Structure-activity relationship of biphalin. The synthesis and biological activities of new analogs with modifications in positions 3 and 4
AUTHOR(S): Misicka, Aleksandra; Lipkowski, Andrzej W.; Horvath, Robert; Davis, Peg; Porreca, Frank; Yamamura, Henry I.; Hruby, Victor J.
CORPORATE SOURCE: Dep. Chem. Pharmacol., Univ. Arizona, Tucson, AZ, 85721, USA
SOURCE: Life Sciences (1997), 60(15), 1263-1269
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB New analogs of biphalin [(Tyr-D-Ala-Gly-Phe-NH-)2] with modifications of amino acid residues in positions 3,3' and 4,4' have been synthesized. The potency and selectivity of these analogs were evaluated by competitive radioreceptor binding assay in the rat brain using [3H]CTOP (mu ligand) and [3H][p-Cl-Phe4]DPDPE (delta ligand) as ligands, and by bioassay in the mouse vas deferens (MVD, delta receptor assay) and guinea pig ileum (GPI, mu receptor assay). The sym. substitution of phenylalanine in positions 4 and 4' with p-





fluorophenylalanine or p-nitrophenylalanine resulted in an enhancement of the affinity at both delta and mu receptors, with some increase of the selectivity for delta opioid receptors. The analog containing p-chlorophenylalanine in positions 4 and 4' is the most selective to the delta receptors in this series, with a selectivity ratio about 5. The sym. substitution of the glycine-3 residue with phenylalanine resulted in a decrease of binding affinities and biol. potencies at both μ & γ receptors.

IT 151608-19-4P 155482-41-0P 155482-42-1P
155482-43-2P 189169-89-9P 189169-93-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and biol. activities of biphalin analogs)

RN 151608-19-4 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-chloro-, 2-(L-tyrosyl-D-alanylglycyl-4-chloro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

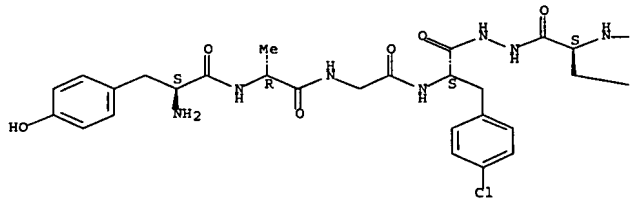
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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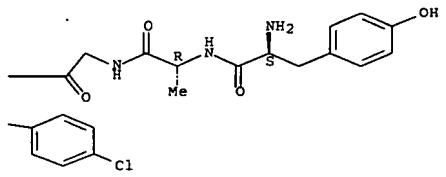


RN 155482-41-0 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-iodo-, 2-(L-tyrosyl-D-alanylglycyl-4-iodo-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

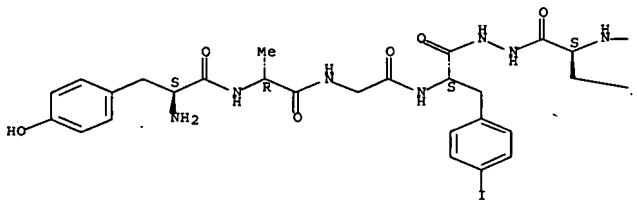
NTE multichain
modified

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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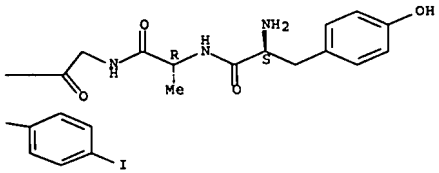


RN 155482-42-1 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-amino-, 2-(L-tyrosyl-D-alanylglycyl-4-amino-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified

SEQ 1 YAGF

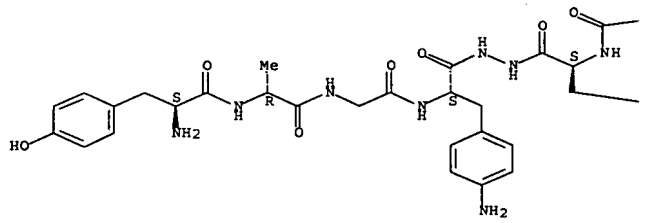
1 YAGF





Absolute stereochemistry.

PAGE 1-A



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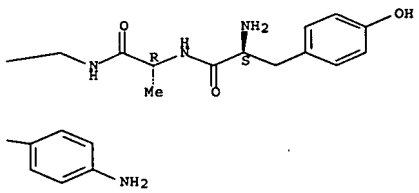


RN 155482-43-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-nitro-, 2-(L-tyrosyl-D-alanylglycyl-4-nitro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

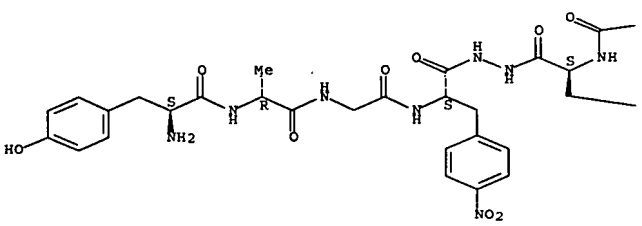
NTE multichain
modified

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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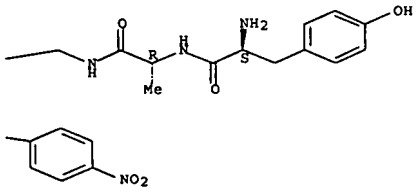


RN 189169-89-9 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-fluoro-, 2-(L-tyrosyl-D-alanylglycyl-4-fluoro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

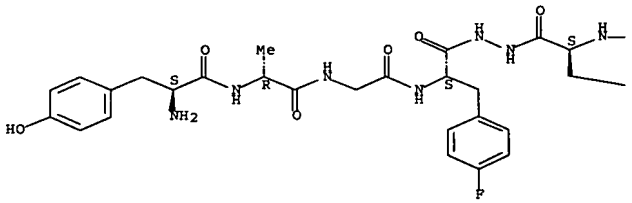
1 YAGF

Absolute stereochemistry.





PAGE 1-A



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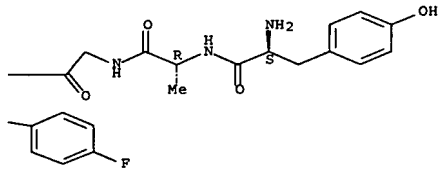


RN 189169-93-5 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-fluoro-, 2-(L-tyrosyl-D-alanylglycyl-4-fluoro-L-phenylalanyl)hydrazide, monohydrochloride (9CI) (CA INDEX NAME)

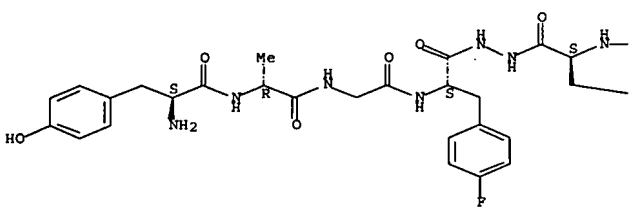
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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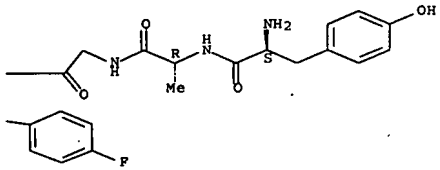


IT 189169-92-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and biol. activities of biphalin analogs)
RN 189169-92-4 CAPLUS
CN L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl-D-alanylglycyl-4-fluoro-, 2-[N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl-D-alanylglycyl-4-fluoro-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

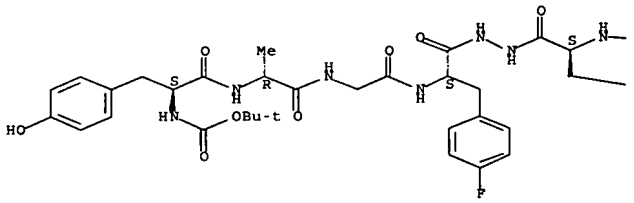
1 YAGF

Absolute stereochemistry.





PAGE 1-A



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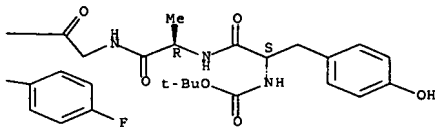


L41 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:695829 CAPLUS Full-text
DOCUMENT NUMBER: 126:26372
TITLE: A systematic investigation of factors that enhance penetration of peptides across the blood brain barrier
AUTHOR(S): Hruby, V. J.; Davis, T. P.; Polt, R.; Bartosz-Bechowski, H.; Misicka, A.; Lipkowski, A.; Sharma, S. D.; Li, G.; Bonner, G.; et al.
CORPORATE SOURCE: Departments Chemistry, University Arizona, Tucson, AZ, 85721, USA
SOURCE: Peptides: Chemistry, Structure and Biology, Proceedings of the American Peptide Symposium, 14th, Columbus, Ohio, June 18-23, 1995 (1996), Meeting Date 1995, 154-156. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Mayflower Scientific: Kingswinford, UK.
CODEN: 63NTAF
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A systemic approach to enhance penetration of peptides across the blood brain barrier (BBB) is discussed. The approach includes the following major components: (1) develop highly selective ligands for brain receptor types and subtypes, (2) utilizing conformational constraint and other structural modifications to stabilize peptides against proteolytic degradation, (3) establish structural peptides (consensus sequences) that can be appended to stable, receptor selective ligands at ancillary sites and that can serve as specific sites of cleavages in the brain prodrug approach, (4) systematically investigate lipophilicity, amphiphilicity, and dynamics as approaches to enhancing penetration of the BBB, (5) evaluate mechanisms for keeping peptides in circulation, and (6) evaluate the use of putative carrier-mediated

mechanisms such as lipid transporters, glucose transporters, polycation transporters, etc. for passage of peptide conjugates through the BBB.

IT 151608-19-4
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(peptide structure in relation to penetration across blood brain barrier)

RN 151608-19-4 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-chloro-, 2-(L-tyrosyl-D-alanylglycyl-4-chloro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

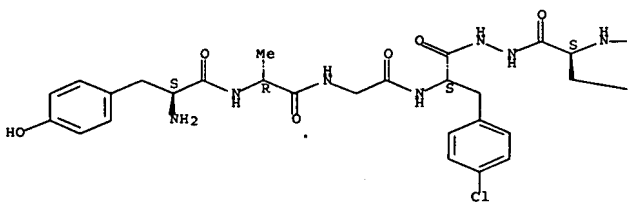
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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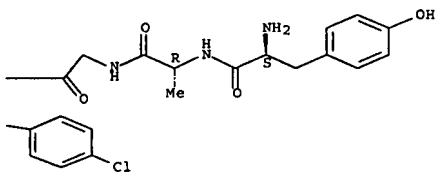


L41 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:170363 CAPLUS Full-text
DOCUMENT NUMBER: 124:277977





TITLE: Blood-to-central nervous system entry and stability of biphalin, a unique double-enkephalin analog, and its halogenated derivatives

AUTHOR(S): Abbruscato, T. J.; Williams, S. A.; Misicka, A.; Lipkowski, A. W.; Hruby, V. J.; Davis, T. P.

CORPORATE SOURCE: Coll. Med., Univ. Arizona, Tucson, AZ, 85724, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 276(3), 1049-57
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Biphalin (Tyr-D-Ala-Gly-Phe-NH)2 is a unique opioid peptide analog that contains two active enkephalin pharmacophores and is more potent than morphine and etorphine in eliciting analgesia after intrathecal administration. After systemic administration, only a small amount was detected in the brain, but analgesia was observed Because halogenation of enkephalin analogs has been shown to increase the brain uptake after systemic administration, the research group synthesized both p-[Cl-Phe4,4']biphalin and p-[F-Phe4,4']biphalin. The aim of the present study was to characterize and compare the blood-to-central nervous system (CNS) pharmacokinetics and biol. stability of biphalin and related halogenated analogs. The initial screening used an in vitro blood-brain barrier model and identified p-[Cl-Phe4,4']biphalin as the enkephalin analog with the best potential for greater CNS entry. The CNS uptake and stability of biphalin and p-[Cl-Phe4,4']biphalin was examined further using an in situ brain perfusion technique coupled to high-performance liquid chromatog. anal. Both biphalin and its chlorohalogenated analog, were found to significantly enter the CNS through both the blood-brain and blood-cerebrospinal fluid barriers. Chlorohalogenation of biphalin was shown to both improve CNS entry, most likely through an enhancement in lipophilicity, and increase biol. stability. This study suggests that incorporation of chlorohalogens at the p-Phe4,4' position is a promising structural modification in the development of biphalin as a successful opioid drug for the clinic.

IT 151608-19-4
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(blood-to-central nervous system entry and stability of biphalin, a unique double-enkephalin analog, and its halogenated derivs.)

RN 151608-19-4 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-chloro-, 2-(L-tyrosyl-D-alanylglycyl-4-chloro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

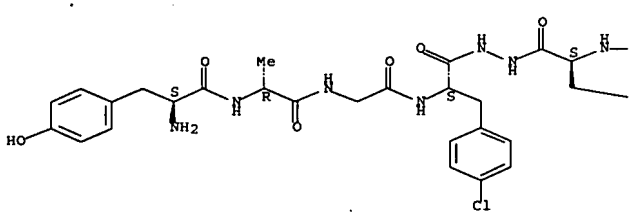
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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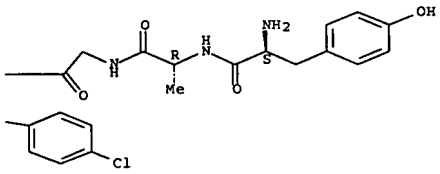


L41 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:450250 CAPLUS Full-text
DOCUMENT NUMBER: 121:50250
TITLE: Structure-activity relationships of analogs of highly potent opioid peptide, biphalin
AUTHOR(S): Misicka, Aleksandra; Lipkowski, Andrzej W.; Horvath, Robert; Davis, Peg; Porreca, Franc; Yamamura, Henry I.; Hruby, Victor J.
CORPORATE SOURCE: Dep. Chem. Pharmacol., Univ. Arizona, Tucson, AZ, 85721, USA
SOURCE: Regulatory Peptides (1994), (Suppl. 1), S131-S132
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English

AB For SAR study of biphalin {(Tyr-D-Ala-Gly-PheNH-)2} the authors have synthesized several analogs with modifications of amino acid residues in position 3 and 4. The introduction of halogenated phenylalanine residues in position 4 increases affinity to δ-receptors. Introducing basic aromatic amino acid residues in position 4 resulted in decrease in affinity to μ-receptors, but preserve affinity to δ-receptors.

IT 155482-41-0 155482-42-1 155482-43-2
RL: PROC (Process)
(opioid receptors binding of, mol. structure in relation to)

RN 155482-41-0 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-iodo-, 2-(L-tyrosyl-D-





alanylglycyl-4-iodo-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

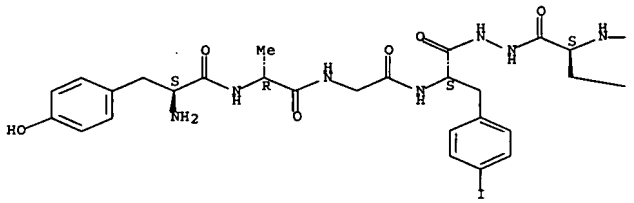
NTE multichain
modified

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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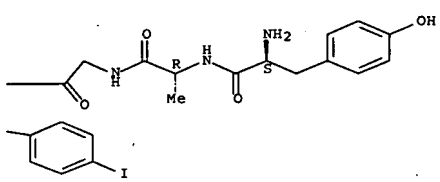


RN 155482-42-1 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-amino-, 2-(L-tyrosyl-D-alanylglycyl-4-amino-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

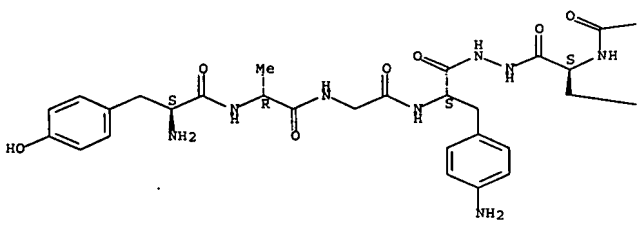
NTE multichain
modified

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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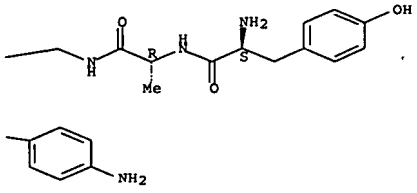


RN 155482-43-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-nitro-, 2-(L-tyrosyl-D-alanylglycyl-4-nitro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified

SEQ 1 YAGF

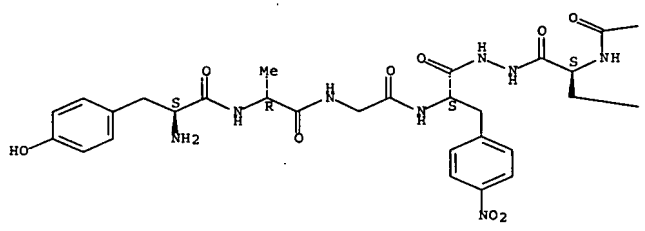
1 YAGF

Absolute stereochemistry.





PAGE 1-A



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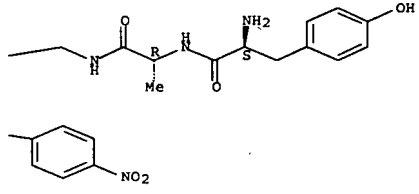


L41 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:712 CAPLUS Full-text
DOCUMENT NUMBER: 120:712
TITLE: Assessment of an in vitro blood-brain barrier model using several [Met5]enkephalin opioid analogs
AUTHOR(S): Weber, Steven J.; Abbruscato, Thomas J.; Brownson, E. A.; Lipkowski, Andrzej W.; Polt, Robin; Misicka, Aleksandra; Haaseth, Ronald C.; Bartosz, Hubert; Hruby, Victor J.; Davis, Thomas P.
CORPORATE SOURCE: OREAD Lab., Inc., Lawrence, KS, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 266(3), 1649-55
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Confluent monolayers of primary and continuous passaged cultures of bovine brain microvessel endothelial cells (BMEC) have been suggested to model the blood-brain barrier (BBB). Increased lipophilicity has been previously suggested to increase BBB penetration. The intent of this study was to examine the effect that structural modifications of the [Met5]enkephalin analog DPDPE had on lipophilicity and passage across the BMEC. The BMEC consisted of a monolayer of confluent primary BMEC grown on polycarbonate (10 μm) filters. Permeability coeffs. were calculated on the basis of the

diffusion of peptides across the BMEC in a Side-Bi-Side diffusion chamber. Lipophilicity of the peptides examined was determined by using reversed-phase HPLC and calculating the capacity factor (k). Diffusion across the BMEC (for all peptides examined) was linear from 15 to 120 min; therefore, these time points were used to calculate permeability coeffs. Permeability coeffs. ranged from 14.34 to 92.00 cm/min (+ 10-4), with [p-ClPhe4,4']biphalin being the highest. Anal. of variance coupled with the Newman-Keuls test showed greater passage of select peptide analogs across the BMEC, including [p-ClPhe4,4']biphalin, [p-ClPhe4]DPDPE and reduced DPDPE. Interestingly, upon passage across the confluent monolayer, reduced DPDPE was converted to cyclized DPDPE. Calculated HPLC k ranged from 3.82 to 12.50. The most lipophilic peptide (highest) examined was acetylated Phe0-DPDPE. Anal. of the regression line of permeability coeffs. plotted against k yielded a correlation coefficient of 0.745. The data provided in this study offer strong evidence that increasing peptide lipophilicity enhances passage across the BMEC. The greatest BMEC permeability coeffs., though not the greatest k, were obtained with peptides having a chlorohalogenation at the Phe4 residue, suggesting that factors other than lipophilicity may play a role in BMEC passage. Comparison of the permeability coeffs. obtained from the BMEC system with those obtained from in vivo BBB studies suggest that the BMEC system may be very useful in predicting peptide (analog) passage across the in vivo BBB.

IT 151608-19-4
RL: BIOL (Biological study)
(blood-brain barrier permeability to, lipophilicity in relation to)

RN 151608-19-4 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-4-chloro-, 2-(L-tyrosyl-D-alanylglycyl-4-chloro-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

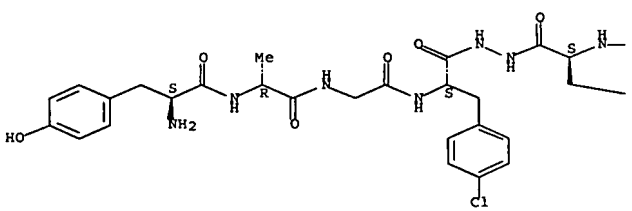
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A







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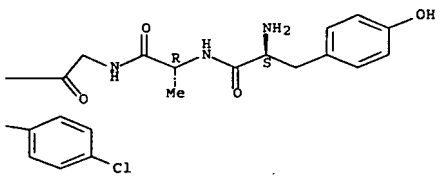

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L42  ANSWER 1 OF 23  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2006:408824  CAPLUS  Full-text
DOCUMENT NUMBER:          144:391395
TITLE:                    Preparation of novel peptide derivatives as analgesics
INVENTOR(S):              Lipkowski, Andrzej; Misicka-Kesik,
                          Aleksandra; Hruby, Victor
PATENT ASSIGNEE(S):       Pol.
SOURCE:                   Pol., 8 pp.
                          CODEN: POXXA7
DOCUMENT TYPE:            Patent
LANGUAGE:                 Polish
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
     --------------       ----   --------    --------------------   --------
     PL 189753             B1    20050930    PL 1998-329663         19981112
PRIORITY APPLN. INFO.:                       PL 1998-329663         19981112
OTHER SOURCE(S):          CASREACT 144:391395; MARPAT 144:391395
GI
```

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title peptides containing guanidine group I [R = CH2Ph, 3-indolylmethyl] and II [Me, CH(OH)Me, CH2OH, (CH2)3NHC(:NH)NH2, (CH2)4NH2], useful as analgesics, were prepared Thus, treating Tyr-Pro-Phe-Phe-NH2 hydrochloride with S-methylthiourea and tetramethylguanidine in DMF afforded I.HCl [R = Ch2Ph] which showed analgesic activity in rat at 1 mg/kg.

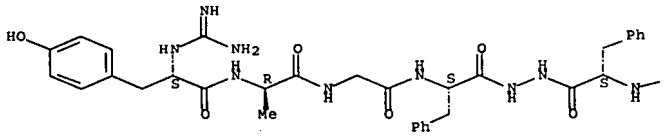
IT 883229-21-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel peptide derivs. as analgesics)

RN 883229-21-8 CAPLUS

CN L-Phenylalanine, N-(aminoiminomethyl)-L-tyrosyl-D-alanylglycyl-, 2-[N-(aminoiminomethyl)-L-tyrosyl-D-alanylglycyl-L-phenylalanyl]hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

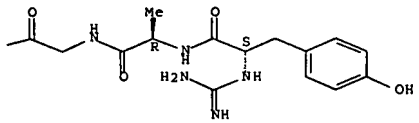
Absolute stereochemistry.

PAGE 1-A



●2 HCl

PAGE 1-B



IT 83852-32-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of novel peptide derivs. as analgesics)

RN 83852-32-8 CAPLUS

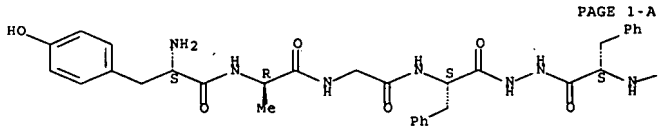
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.





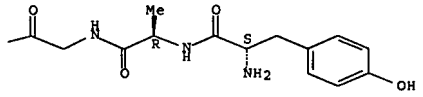
PAGE 1-A



●2 HCl

YAGF

PAGE 1-B



L42 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:62536 CAPLUS Full-text

DOCUMENT NUMBER: 144:460668

TITLE: Antinociception after intrathecal biphalin application in rats: a reevaluation and novel, rapid method to confirm correct catheter tip position

AUTHOR(S): Kosson, Dariusz; Bonney, Iwona; Carr, Daniel B.; Mayzner-Zawadzka, Ewa; Lipkowski, Andrzej W.

CORPORATE SOURCE: Medical Research Centre, Polish Academy of Sciences, Warsaw, PL 02-106, Pol.

SOURCE: Pharmacological Reports (2005), 57(4), 545-549
CODEN: PRHEDU; ISSN: 1734-1140

PUBLISHER: Polish Academy of Sciences, Institute of Pharmacology

DOCUMENT TYPE: Journal

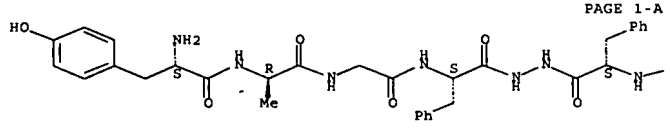
LANGUAGE: English

AB The opioid peptide dimmer biphalin [(Tyr-D-Ala-Gly-Phe-NH-)2] has high potency both in vivo and in vitro. Its antinociceptive activity depends on the route of administration: the lowest potency is after s.c., and the highest after intrathecal or inracerebroventricular administration. We tested the analgesic activity of biphalin in a wide range of doses after intrathecal administration to rats. Doses as low as 0.005 nmol produced significant analgesia. Increasing the dose up to 2 nmol elevated and prolonged antinociception without any evident side effects, indicating that biphalin is an extremely potent opioid after intrathecal application with a wide therapeutic window. The highest dose tested (20 nmol) produced full analgesia and body rigidity lasting 2-3 h. After muscle tone returned to normal, antinociception lasted for several more hours. During these studies we observed a correlation between responses to biphalin and catheter placement. Postmortem verification of catheter placement revealed that in those rats in which high-dose biphalin did not produce analgesia or muscle rigidity, the catheter was positioned incorrectly or the flow of drug solution was obstructed. Therefore, a secondary conclusion is that assessment of transient rigidity after administration of a high dose of biphalin may be used as an easy method to confirm intrathecal placement of the catheter.

IT 83916-01-2, Biphalin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biphalin injected intrathecally produced dose-dependent antinociceptive effect and high dose produced full analgesia, body rigidity which correlated with catheter placement in rat)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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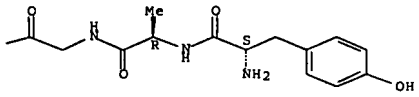
PAGE 1-B



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:143180 CAPLUS Full-text
DOCUMENT NUMBER: 140:193082
TITLE: New compounds and their analgesic applications
INVENTOR(S): Lipkowski, Andrzej W.; Carr, Daniel ; Bonney, Iwona; Kosson, Dariusz; Misiecka-Kesik, Aleksandra
PATENT ASSIGNEE(S): Pol.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2004014943 | A2 | 20040219 | WO 2003-PL77 | 20030807 |
| WO 2004014943 | A3 | 20040429 | | |

PCT/PL03

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| US 2006241053 | A1 | 20061026 | US 2006-524343 | 20060130 <-- |
| PRIORITY APPLN. INFO.: | | | PL 2002-355470 | A 20020813 |
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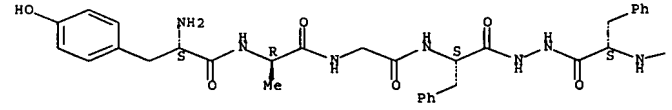
OTHER SOURCE(S): MARPAT 140:193082
AB Application of peptides with analgesic properties as the active ingredient in devices for the direct application of medication to the site of their expected analgesic activity, particularly in the central nervous system, is disclosed.
IT 83916-01-2 88191-65-5 659732-80-6
659732-81-7 659732-82-8 659732-83-9
659732-84-0 659732-85-1 659732-86-2
659732-87-3 659732-88-4 659732-89-5
659732-90-8
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(application of analgesic peptides)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

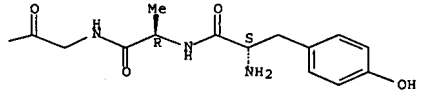
Absolute stereochemistry.

PAGE 1-A



YAGF

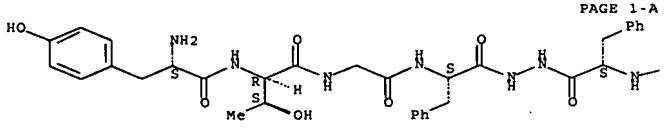
PAGE 1-B



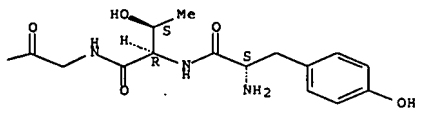
RN 88191-65-5 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-threonylglycyl-, 2-(L-tyrosyl-D-threonylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



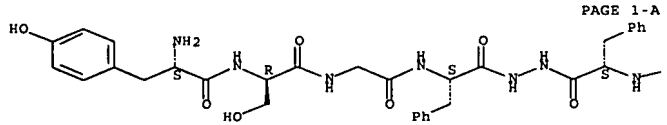
PAGE 1-B



RN 659732-80-6 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-serylglycyl-, 2-(L-tyrosyl-D-serylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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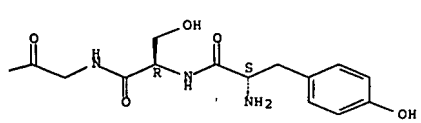


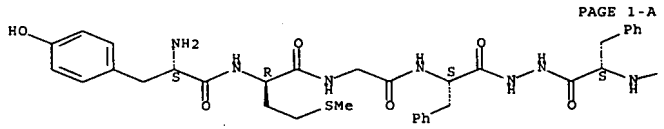
RN 659732-81-7 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-methionylglycyl-, 2-(L-tyrosyl-D-methionylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

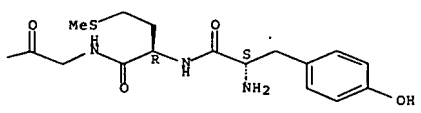




PAGE 1-A



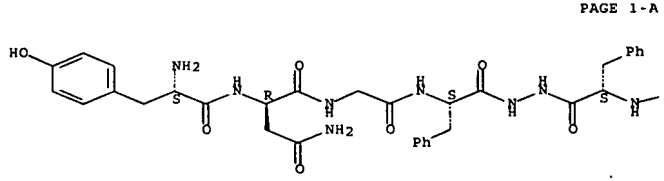
PAGE 1-B



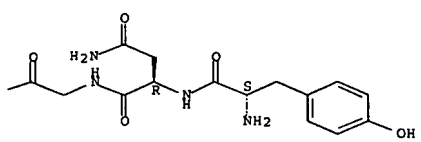
RN 659732-82-8 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-asparaginylglycyl-, 2-(L-tyrosyl-D-asparaginylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



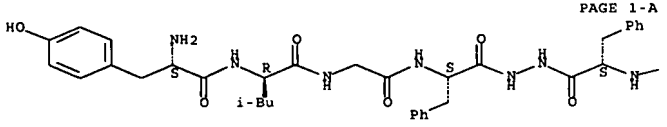
PAGE 1-B



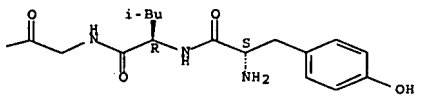
RN 659732-83-9 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-leucylglycyl-, 2-(L-tyrosyl-D-leucylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



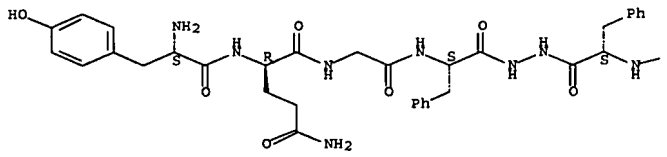
PAGE 1-B



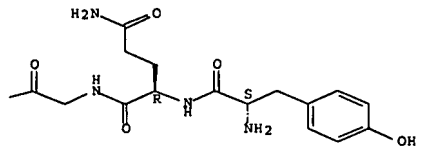
RN 659732-84-0 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-glutaminylglycyl-, 2-(L-tyrosyl-D-glutaminylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



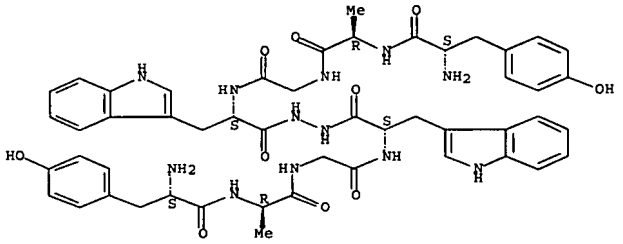
RN 659732-85-1 CAPLUS
CN L-Tryptophan, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-





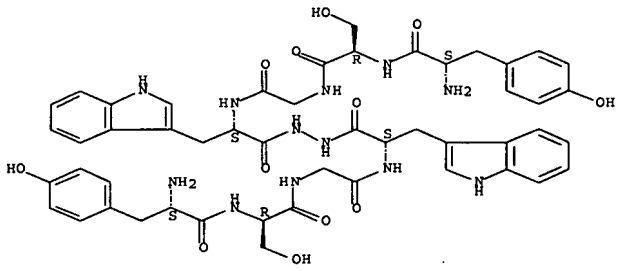
tryptophyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



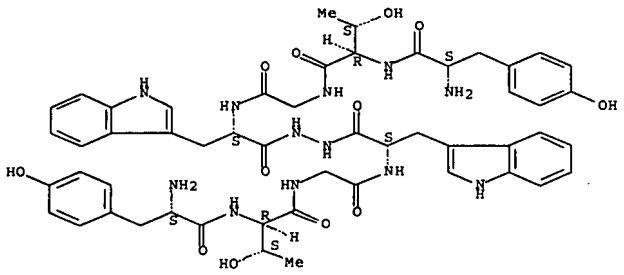
RN 659732-86-2 CAPLUS
CN L-Tryptophan, L-tyrosyl-D-serylglycyl-, 2-(L-tyrosyl-D-serylglycyl-L-tryptophyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



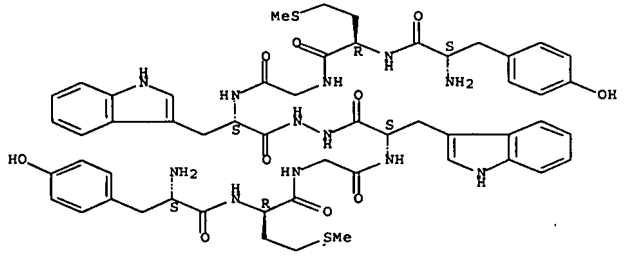
RN 659732-87-3 CAPLUS
CN L-Tryptophan, L-tyrosyl-D-threonylglycyl-, 2-(L-tyrosyl-D-threonylglycyl-L-tryptophyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 659732-88-4 CAPLUS
CN L-Tryptophan, L-tyrosyl-D-methionylglycyl-, 2-(L-tyrosyl-D-methionylglycyl-L-tryptophyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

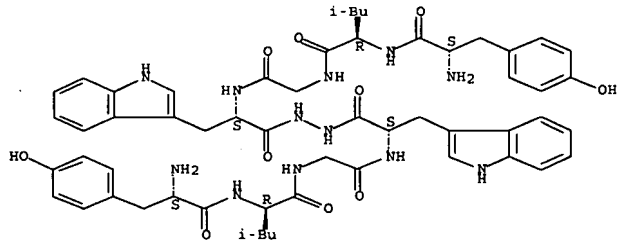


RN 659732-89-5 CAPLUS
CN L-Tryptophan, L-tyrosyl-D-leucylglycyl-, 2-(L-tyrosyl-D-leucylglycyl-L-tryptophyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



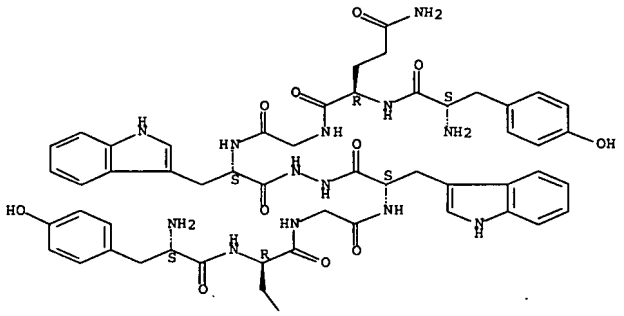




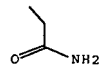
RN 659732-90-8 CAPLUS
CN L-Tryptophan, L-tyrosyl-D-glutaminylglycyl-, 2-(L-tyrosyl-D-glutaminylglycyl-L-tryptophyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



L42 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:717510 CAPLUS Full-text
DOCUMENT NUMBER: 139:235424
TITLE: Pharmaceutical compositions containing polymers and analgesics and anesthetics
INVENTOR(S): Carr, Daniel B.; Lipkowski, Andrzej

W.; Wise, Donald L.; Hasirci, Vasif
PATENT ASSIGNEE(S): New England Medical Hospitals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 26 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003170288 | A1 | 20030911 | US 2002-213584 | 20020806 |
| US 6913760 | B2 | 20050705 | | |

PRIORITY APPLN. INFO.: US 2001-310434P P 20010806

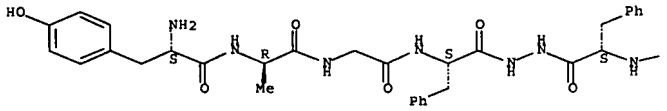
AB The invention provides a drug delivery compns. and methods for treating pain. A drug delivery composition contains a polymer and at least 2 drugs such as an analgesic and an anesthetic. PLGA rods were prepared by converting polymer to a foam, which was ground, sieved and mixed overnight with drug. The PLGA was formulated as a 85:15 copolymer. The polymer-drug mix was extruded under pressure. Rods were introduced intrathecally into rats using a silicone catheter. Release of hydromorphone, bupivacaine and biphalin was studied. Drug release studies showed that BP was released faster than the other two drugs with HM being the slowest. Release was almost zero order for BP and HM. Biphalin release occurred in two phases.

IT 83916-01-2, Biphalin
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing polymers and analgesics and anesthetics)

RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

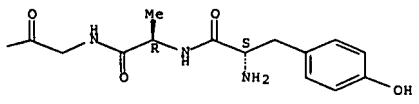
Absolute stereochemistry.

PAGE 1-A



YAGF

PAGE 1-B



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN





ACCESSION NUMBER: 2003:157514 CAPLUS Full-text
DOCUMENT NUMBER: 139:312119
TITLE: Antinociceptive effects of hydromorphone, bupivacaine and biphalin released from PLGA polymer after intrathecal implantation in rats
AUTHOR(S): Sendil, D.; Bonney, I. Maszczynska; Carr, D. B.; Lipkowski, A. W.; Wise, D. L.; Hasirci, V.
CORPORATE SOURCE: Departments of Biological Sciences and Biotechnology, Biotechnology Research Unit, Middle East Technical University, Ankara, 06531, Turk.
SOURCE: Biomaterials (2003), 24(11), 1969-1976
CODEN: BIMADU; ISSN: 0142-9612
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

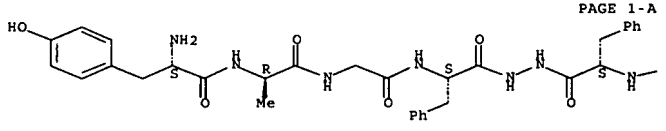
AB Intraspinal drug delivery, based on the concept of controlling pain by delivering drug to a nociceptive target rich in opioid and other relevant receptors is increasingly used clin. The therapeutic ratio for opioids or other centrally acting agents is potentially greater if they are administered intrathecally (i.t.) than outside the central nervous system (CNS). The present study was designed with the ultimate goal of formulating a controlled release system for intrathecal analgesia characterized by effectiveness, rapid onset and few side effects for chronic pain control. A biodegradable copolymer poly(l-lactide-co- glycolide) (PLGA) was used to prepare a rod-shaped drug delivery system containing hydromorphone (HM), bupivacaine (BP), both HM and BP, or biphalin (BI). In vitro drug release kinetics of these systems showed a zero-order release rate for HM and BP from PLGA (85:15) rods. Drug-loaded rods were implanted i.t. Control groups received only placebo implants. Measurement of analgesic efficacy was carried out with tail flick and paw-withdrawal tests. In vivo studies showed potent, prolonged analgesia in comparison to controls for all active treatments. Analgesic synergy was observed with HM and BP. With further refinements of drug release rate, these rods may offer a clin. relevant alternative for intrathecal analgesia.

IT 83916-01-2, Biphalin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antinociceptive effects of hydromorphone, bupivacaine, and biphalin released from PLGA polymer after intrathecal implantation in rats)

RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

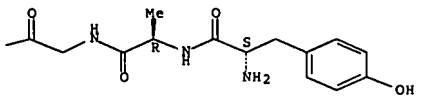
Absolute stereochemistry.

PAGE 1-A



YAGF

PAGE 1-B



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:231047 CAPLUS Full-text
DOCUMENT NUMBER: 136:380280
TITLE: Crystal structure of biphalin sulfate: a multireceptor opioid peptide
AUTHOR(S): Flippen-Anderson, J. L.; Deschamps, J. R.; George, C.; Hruby, V. J.; Misicka, A.; Lipkowski, A. W.
CORPORATE SOURCE: Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC, 20375-5000, USA
SOURCE: Journal of Peptide Research (2002), 59(3), 123-133
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Biphalin is a dimeric opioid peptide, composed of two tetrapeptides connected "tail-to-tail", that exhibits a high affinity for all three opioid receptor types (i.e. μ, δ and κ). This study presents the X-ray crystal structure of biphalin sulfate and compares it to other opioids that interact with the same biol. targets. Both halves of the mol. have a folded backbone conformation but differ significantly from one another. Residues 1-4 in biphalin, which compare well with the δ selective opioid peptide DADLE, fold into a random coil. Residues 5-8, which can be fit to the μ selective peptide D-TIPP-NH2, exhibit a fairly normal type III' β bend. Biphalin also exhibits structural similarities with two naltrexone analogs, naltrexonazine and norbinaltorphamine, that are specific to μ and κ receptor sites.

IT 426828-17-3
RL: PRP (Properties)
(crystal structure of multireceptor opioid peptide biphalin sulfate)
RN 426828-17-3 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide, sulfate (1:1) (salt), decahydrate (9CI) (CA INDEX NAME)

CM 1

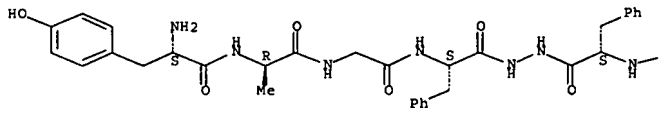
CRN 83916-01-2
CMF C46 H56 N10 O10

Absolute stereochemistry.



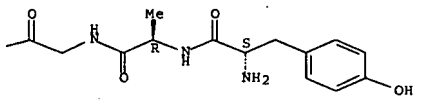


PAGE 1-A



YAGIF

PAGE 1-B



CM 2

CRN 7664-93-9
CMF H2 O4 S

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:552419 CAPLUS Full-text
DOCUMENT NUMBER: 135:313550
TITLE: The opioid peptide analogue biphalin induces less physical dependence than morphine
AUTHOR(S): Yamazaki, Mitsuaki; Suzuki, Tsutomu; Narita, Minoru; Lipkowski, Andrzej W.
CORPORATE SOURCE: Intensive Care Unit, Toyama Medical and Pharmaceutical University Hospital, Toyama, 930-0194, Japan
SOURCE: Life Sciences (2001), 69(9), 1023-1028
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We compared the phys. dependence liability of biphalin, a dimeric enkephalin analog that possesses high antinociceptive activity, with that of morphine in equipotent i.v. doses. Naloxone challenge produced severe withdrawal signs after a 5-day infusion of morphine but only minor withdrawal signs after a 5-day biphalin infusion. In a cross-dependence study, biphalin did not suppress body weight loss after morphine withdrawal, but successfully suppressed weight loss after pentazocine withdrawal. These data support consideration of

biphalin as a new analgesic with a novel pharmacol. profile and min. dependence liability.

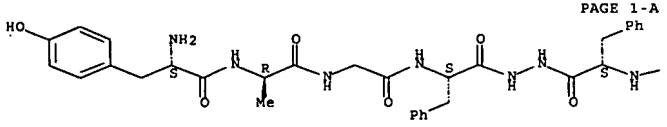
IT 83916-01-2, Biphalin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biphalin induces less phys. dependence than morphine)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

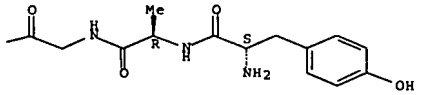
Absolute stereochemistry.

PAGE 1-A



YA GF

PAGE 1-B



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:637734 CAPLUS Full-text

DOCUMENT NUMBER: 134:25553

TITLE: Influence of opioids on lymphocyte circulation and homing

AUTHOR(S): Maksymowicz, M.; Kosson, D.; Lipkowski, A. W.; Olszewski, W. L.

CORPORATE SOURCE: Surgical Research and Transplantology Department, Polish Acad. Sci., Warsaw, Pol.

SOURCE: Transplantation Proceedings (2000), 32(6), 1395-1396
CODEN: TRPPA8; ISSN: 0041-1345

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors investigated the influence of morphine and biphalin administered i.v. and intrathecally to rats on lymphocyte distribution using an in vivo migration test. I.v. administration of biphalin increased lymphocyte extravasation, but decreased lymphocyte homing to lymph nodes and their release to the lymph. Intrathecal biphalin had a similar effect on lymphocyte migration and distribution. I.v. administration of morphine decreased lymphocyte extravasation, whereas intrathecal administration decreased lymphocyte homing to mesenteric lymph nodes. This may suggest the different





effects of opioid peptides on lymphocyte recruitment and mobilization owing to their central or peripheral interaction with specific receptors.

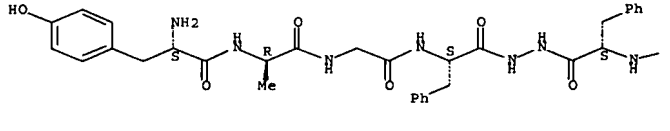
IT 83916-01-2, Biphalin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(biphaline and morphine effects on lymphocyte circulation and homing)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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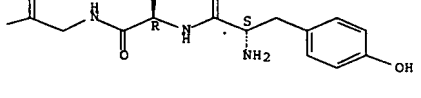
PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:639903 CAPLUS Full-text

DOCUMENT NUMBER: 132:516

TITLE: Biological activity of fragments and analogues of the potent dimeric opioid peptide, biphalin

AUTHOR(S): Lipkowski, Andrzej W.; Misicka, Aleksandra; Davis, Peg; Stropova, Dagmar; Janders, Jacqueline; Lachwa, Magdalena; Porreca, Frank; Yamamura, Henry I.; Hruby, Victor J.

CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (1999), 9(18), 2763-2766
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

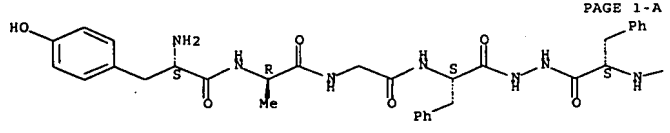
LANGUAGE: English

AB The synthesis and biol. activity of two fragments of the very potent opioid peptide biphalin, showed that Tyr-D-Ala-Gly-Phe-NH-NH<-Phe is the minimal fragment necessary to express equal affinities and the same biol. activity profile as the parent biphalin. The replacement of N'-Phe with other L- or D-lipophilic amino acids showed the possibility of modification of receptor efficacy of the analogs.

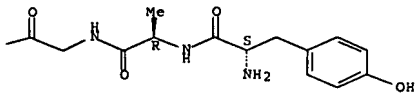
IT 83916-01-2DP, Biphalin, analogs
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(biol. activity of biphalin fragments and analogs)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:578884 CAPLUS Full-text
DOCUMENT NUMBER: 131:346698
TITLE: Identification of the structural elements responsible for high biological activity of dimeric opioid peptide biphalin
AUTHOR(S): Misicka, A.; Lipkowski, A. W.; Stropova, D.; Yamamura, H. I.; Davis, P.; Porreca, F.; Hruby, V. J.
CORPORATE SOURCE: Departments of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Peptide Science: Present and Future, Proceedings of the International Peptide Symposium, 1st, Kyoto, Nov. 30-Dec. 5, 1997 (1999), Meeting Date 1997, 726-727. Editor(s): Shimonishi, Yasutsugu. Kluwer: Dordrecht, Neth.
CODEN: 68BYA5
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The study of the metabolism of biphalin indicated that des(Tyr-D-Ala-Gly)biphalin (AA232) could be one of the major metabolite of biphalin. Therefore the authors synthesized de novo resp. peptide (AA232) and its analogs for evaluation of biol. activities and structural studies. The results suggest that the pharmacophore responsible for the biol. properties of

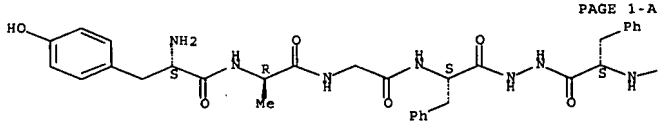




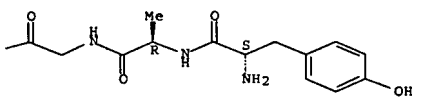
biphalin is one tetrapeptide extended with a hydrazide bridge and an aromatic amino acid residue (Phe4') on the other side of this bridge. In consequence the pharmacophore of biphalin will combine one phenol and amino group of Tyr(1), and two Ph rings of Phe(4) and Phe(4'). To compare the topog. relations of the aromatic rings, the authors have synthesized analogs of AA232 in which Phe(4) or Phe(4') have been replaced with tryptophan. The receptor binding and biol. activities of the resulting analog with tryptophan in position 4' are similar to the parent compound AA232. The replacement of Phe(4) with Trp resulted in a ten-fold decrease in the biol. activity of both but without significant changes in receptor binding properties.
IT 83916-01-2, Biphalin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(identification of structural elements responsible for high biol. activity of dimeric opioid peptide biphalin)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:688054 CAPLUS Full-text
DOCUMENT NUMBER: 130:60609
TITLE: Inhibitory effect of biphalin and AZT on murine Friend leukemia virus infection in vitro
AUTHOR(S): Tang, Jie-Liu; Lipkowski, Andrzej W.; Specter, Steven
CORPORATE SOURCE: Department of Medical Microbiology and Immunology, University of South Florida College of Medicine, Tampa, FL, 33612, USA
SOURCE: International Journal of Immunopharmacology (1998), 20(9), 457-466
CODEN: IJIMDS; ISSN: 0192-0561

PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

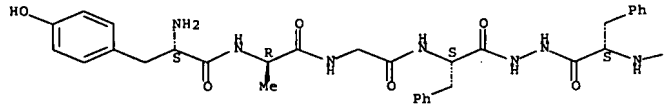
AB Biphalin is a bivalent opioid analog containing two tyrosine residues. The authors have examined the effect of biphalin's anti-retroviral potency in vitro using a murine model. Biphalin, in non-cytotoxic concns., suppressed in a dose-dependent fashion the replication of Friend leukemia virus (FLV) in Mus dunni cells as determined using a focus forming assay. FLV replication was substantially reduced by biphalin at 10-4 M concentration When biphalin was combined with 3'-azido-3'-deoxythymidine (AZT) the two acted synergistically in inhibiting FLV replication compared to either used alone. Using a reverse transcriptase (RT) assay, FLV RT levels also were noted to be reduced in the presence of biphalin. These observations indicate that biphalin possesses anti-retroviral activity in vitro, suggesting that this opioid peptide should be examined further in vivo to determine if it is a candidate for combined therapy with AZT and possibly other drugs for retrovirus infections including the human immunodeficiency virus (HIV).

IT 83916-01-2, Biphalin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(inhibitory effect of biphalin and AZT on murine FLV infection in vitro)

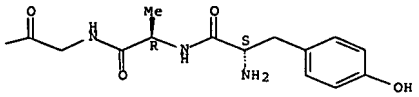
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:169052 CAPLUS Full-text
DOCUMENT NUMBER: 128:290334
TITLE: [125I-Tyr1]biphalin binding to opioid receptors of rat brain and NG108-15 cell membranes
AUTHOR(S): Slaninova, Jirina; Appleyard, Suzanne M.; Misicka,





Aleksandra; Lipkowski, Andrzej W.; Knapp, Richard J.; Weber, Steven J.; Davis, Thomas P.; Yamamura, Henry I.; Hruby, Victor J.
CORPORATE SOURCE: Department of Pharmacology, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Life Sciences (1998), 62(14), PL199-PL204
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

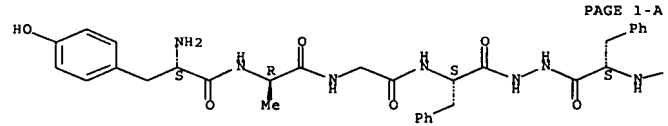
AB Mono iodinated analogs of biphalin [(Tyr-D-Ala-Gly-Phe-NH-)2], both nonradioactive [I-Tyr1]biphalin and radioactive [125I-Tyr1]biphalin have been synthesized. The radioligand binding profiles of these compds. for two types of tissues, rat brain membranes, and NG108-15 cell membranes were identical to the parent biphalin. This is addnl. evidence for the hypothesis that biphalin behaves like a monomeric ligand and that only one intact tyrosine is necessary for high biol. activity. The second tyrosine could be used for successful radioiodination which may greatly simplify biochem. and pharmacol. studies of biphalin. The results of receptor binding studies show that the binding of both biphalin and [I-Tyr1]biphalin to the δ and μ opioid receptors are not independent. [125I-Tyr1]Biphalin binds to δ receptors as shown in NG108-15 cell membranes. Nevertheless, [125I]biphalin binding to δ receptors in rat brain membranes was hardly evident and μ receptor binding predominated or at least was much more readily detectable in this preparation

IT 83916-01-2, Biphalin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mono iodinated biphalin analogs binding to opioid receptors of rat brain and NG108-15 cell membranes)

RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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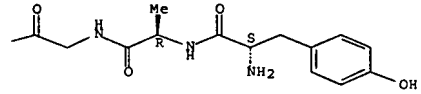


IT 206054-29-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

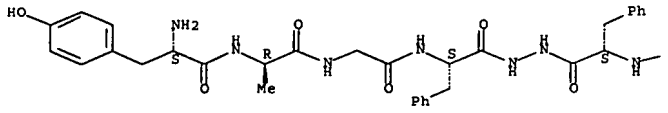
study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mono iodinated biphalin analogs binding to opioid receptors of rat brain and NG108-15 cell membranes)

RN 206054-29-7 CAPLUS

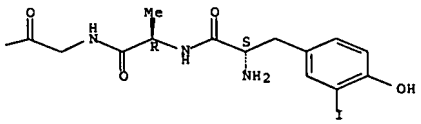
CN L-Phenylalanine, 3-iodo-L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT 206054-30-0P

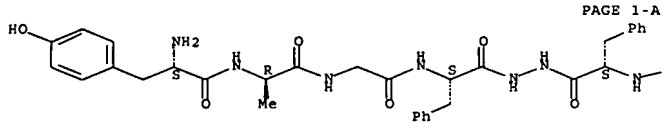
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mono iodinated biphalin analogs binding to opioid receptors of rat brain and NG108-15 cell membranes)

RN 206054-30-0 CAPLUS

CN L-Phenylalanine, 3-(iodo-125I)-L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

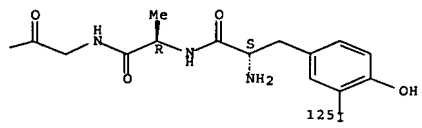
PAGE 1-A







PAGE 1-B



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1994:646062 CAPLUS Full-text

DOCUMENT NUMBER: 121:246062

TITLE: Non-deterministic individual responses to receptor-selective opioid agonists

AUTHOR(S): Lipkowski, Andrzej W.; Carr, Daniel B.; Silbert, Brendan S.; Cepeda, M. Soledad; Osgood, Patricia F.; Szyfelbein, Stanislaw K.

CORPORATE SOURCE: Medical Research Centre, Polish Academy of Sciences, Warsaw, 00-784, Pol.

SOURCE: Polish Journal of Pharmacology (1994), 46(1-2), 29-35
CODEN: PJPAE3; ISSN: 1230-6002

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To assess within a single rat strain individual variability of analgesic responses to sub-ED50 doses of receptor-selective opioids, the authors measured: tail flick latency (TFL) responses after intrathecal (ith) injection of δ-, μ-, and κ-agonists administered serially, TFL and tail pinch latencies (TPch) after i.v. μ- and κ-agonists, and TFL and TPch after i.v. agonists of μ or combined μ + δ selectivity. Mean values in each study confirmed an analgesic response, but individual TFL and TPch responses were chaotic and, within each study, rank order correlations between TFL and TPch values within or between drugs were insignificant. The results suggest a hypothesis that such responses are intrinsically nondeterministic because, resembling other complex dynamic systems, they are generated by stochastic receptor-transmitter interactions that in turn evoke a series of nonlinearly coupled cellular and neural events.

IT 83916-01-2, Biphalin

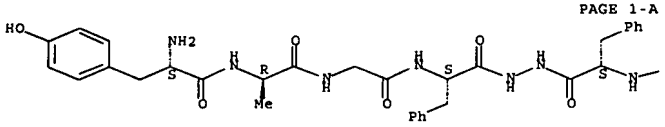
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(analgesic responses to receptor-selective opioids)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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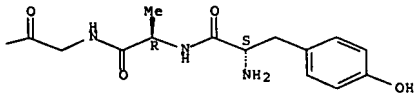


L42 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:261489 CAPLUS Full-text
DOCUMENT NUMBER: 120:261489
TITLE: New opioid compounds in analgesia
AUTHOR(S): Hruby, V. J.; Misicka, A.; Lipkowski, A. W.; Haaseth, R.; Bartosz, H.; Qian, X.; Collins, N.; Meyer, J. P.; Szabo, L.; et al.
CORPORATE SOURCE: Dep. Chem. Pharmacol., Univ. Arizona, Tucson, AZ, 85721, USA
SOURCE: Regulatory Peptides (1994), (Suppl. 1), S71-S72
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using computer assisted design, conformational, and topog. stereostructural considerations, asym. and macrocyclic synthetic chemical, and multiple assays and binding methods the authors have designed conformationally and topog. constrained ligands with high potency, selectivity, and efficacy at δ1-, δ2-, μδcx-, κ1-, and other opioid receptors. The binding of some of these new opioid compds. by δ- and μ-receptors and their ability to inhibit contractions of mouse vas deferens and guinea pig ileum were studied and related to structure.

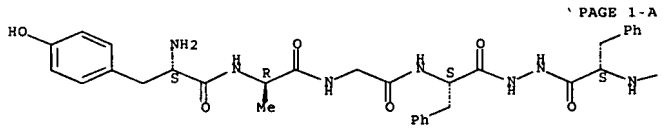
IT 83916-01-2, Biphalin
RL: BIOL (Biological study)
(δ- and μ-opioid receptor binding by and ileum and vas deferens contraction response to, structure in relation to)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.





PAGE 1-A



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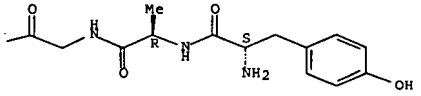


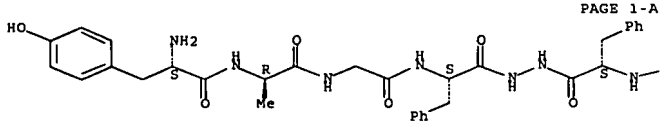
L42 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:208521 CAPLUS Full-text
DOCUMENT NUMBER: 120:208521
TITLE: Spinal co-administration of peptide substance P antagonist increases antinociceptive effect of the opioid peptide biphalin
AUTHOR(S): Misterek, K.; Maszczynska, I.; Dorociak, A.; Gumulka, S. W.; Carr, D. B.; Szyfelbein, S. K.; Lipkowski, A. W.
CORPORATE SOURCE: Dep. Pharmacodyn., Med. Acad., Warsaw, 00927, Pol.
SOURCE: Life Sciences (1994), 54(14), 939-44
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intrathecal injection of 0.25 μg of undecapeptide substance P antagonist (SPA) produced transient antinociception with a peak effect at 5 min. Increasing the SPA dose resulted in neurotoxicity. Intrathecal injection of the opioid peptide biphalin (BIP) produced antinociception for over 3 h without neurotoxicity. Coadministration of SPA (at subtoxic doses) increased BIP's antinociceptive effect. Naltrexone reversed analgesia due to BIP alone as well as after BIP+SPA.

IT 83916-01-2, Biphalin
RL: PRP (Properties)
(antinociceptive effect of, substance P antagonist increase of)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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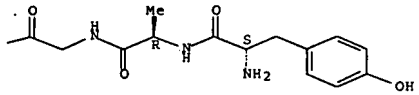


L42 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:670513 CAPLUS Full-text
DOCUMENT NUMBER: 115:270513
TITLE: Enhanced potency of receptor-selective opioids after acute burn injury
AUTHOR(S): Silbert, Brendan S.; Lipkowski, Andrzej W.; Cepeda, M. Soledad; Szyfelbein, Stanislaw K.; Osgood, Patricia F.; Carr, Daniel B.
CORPORATE SOURCE: Dep. Anesth., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SOURCE: Anesthesia & Analgesia (Baltimore, MD, United States) (1991), 73(4), 427-33
CODEN: AACRAT; ISSN: 0003-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dose-response curves of three receptor-selective opioids were established in normal and burned rats. Morphine (μ-agonist), biphalin (μ- and δ-agonist), and U50488H (κ-agonist) analgesia was measured by tail flick latency. Each opioid showed an increase in potency (a decrease in ED50 values) in the burned (15% body surface area) compared with the nonburned groups. Moderate doses of each drug (ED50 estimated from nonburned group data) in each case augmented the stress-induced analgesia in the burned group. Analgesic doses failed to prevent increases in plasma β-endorphin and corticosterone after larger surface area (25%) burns. Regardless of receptor specificity, opioid analgesic potency was increased acutely after burn injuries.

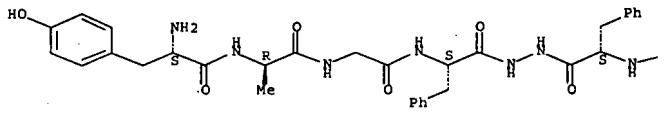
IT 83916-01-2, Biphalin
RL: BIOL (Biological study)
(analgesia from, burn enhancement of)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.





PAGE 1-A



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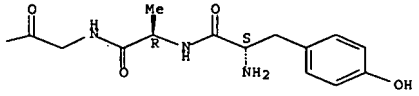


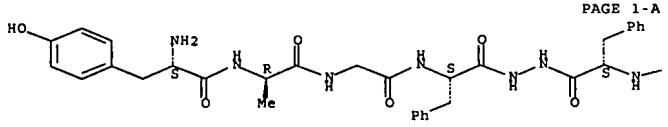
L42 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:422139 CAPLUS Full-text
DOCUMENT NUMBER: 115:22139
TITLE: Analgesic activity of a novel bivalent opioid peptide compared to morphine via different routes of administration
AUTHOR(S): Silbert, B. S.; Lipkowski, A. W.; Cepeda, M. S.; Szyfelbein, S. K.; Osgood, P. F.; Carr, D. B.
CORPORATE SOURCE: Dep. Anesthesia, Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SOURCE: Agents and Actions (1991), 33(3-4), 382-7
CODEN: AGACBH; ISSN: 0065-4299
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The bivalent opioid tetrapeptide biphalin (Tyr-D-Ala-Gly-Phe-NH)2 was synthesized and its analgesic activity was assessed in comparison to morphine in rats. Drugs were administered s.c., i.v., and intrathecally. Tail flick and tail pinch were used as tests for analgesia. Biphalin s.c. showed negligible analgesic activity, but given i.v. it produced significant analgesia, although less potent than morphine via this route. Intrathecal biphalin was more potent than morphine. Biphalin has an intrinsic activity that is apparently compromised by enzymic degradation or redistribution in the periphery, these properties may render it useful in exploring analgesic actions of locally applied opioids in the periphery without unwanted central effects.

IT 83916-01-2, Biphalin
RL: BIOL (Biological study)
(analgesic effects of morphine and, administration route effects on)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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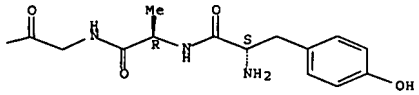


L42 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:211160 CAPLUS Full-text
DOCUMENT NUMBER: 112:211160
TITLE: Peptides as potential antinociceptive drugs
AUTHOR(S): Silbert, Brendan S.; Lipkowski, Andrzej; Carr, Daniel B.; Szyfelbein, Stanislaw K.; Osgood, Patricia F.
CORPORATE SOURCE: Dep. Anesth., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SOURCE: Progress in Clinical and Biological Research (1990), 328(Int. Narc. Res. Conf. (INRC) '89), 485-8
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Biphalin, morphine, and butorphanol were assessed for analgesic activity (tail flick latency) following their administration to rats by various routes. Biphalin, which should be more enzymically resistant than other opioid peptide analogs, was less active than morphine or butorphanol when given s.c. However, biphalin was the most active compound following i.p., i.v., or intrathecal administration. The greatest analgesia was with intrathecal biphalin, and this route also gave the longest duration of action.

IT 83916-01-2, Biphalin
RL: BIOL (Biological study)
(analgesia from, route of administration effect on)

RN 83916-01-2 CAPLUS

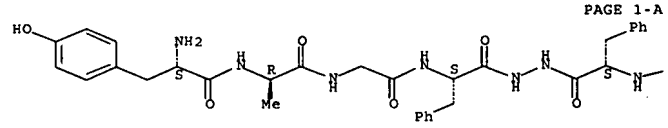
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.





PAGE 1-A



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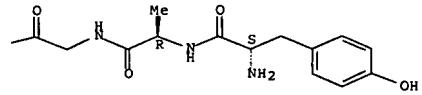


L42 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:199130 CAPLUS Full-text
DOCUMENT NUMBER: 112:199130
TITLE: Preparation of peptides having morphine-like activity
INVENTOR(S): Lipkowski, Andrzej W.
PATENT ASSIGNEE(S): Uniwersytet Warszawski, Pol.
SOURCE: Pol., 4 pp.
CODEN: POXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Polish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PL 131730 | B1 | 19841231 | PL 1981-231571 | 19810609 |
| PRIORITY APPLN. INFO.: | | | PL 1981-231571 | 19810609 |

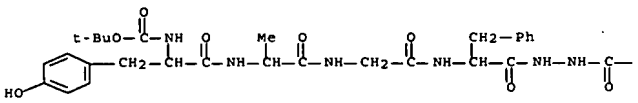
AB (H-Tyr-D-Ala-Gly-Phe-NH)2(CH2)n (I; n = 0, 1-5 integer), having morphine-like activity (no data), are prepared by coupling of X-Tyr-D-Ala-Gly-OH (X = protecting group) with (H-Phe-NH)2(CH2)n at a mole ratio of 2:1. BOC-Tyr-D-Ala-Gly-OH was condensed with (H-Phe-NH)2(CH2)3 at a mole ratio of 2:1 in the presence of N-hydroxybenzotriazole and dicyclohexylcarbodiimide to give 85% (BOC-Tyr-D-Ala-Gly-Phe-NH)2(CH2)3, which was deprotected to give 77% I (n = 3).

IT 83852-31-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deprotection of)

RN 83852-31-7 CAPLUS

CN L-Phenylalanine, N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl]-D-alanyl]glycyl]-, 2-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl]-D-alanyl]glycyl]-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

PAGE 1-A



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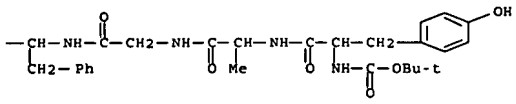


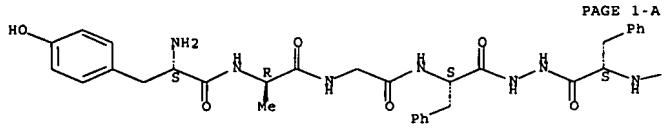
IT 126872-95-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as opioid agonist)
RN 126872-95-5 CAPLUS
CN L-Phenylalanine, N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-, 2-[N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-L-phenylalanyl]hydrazide, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 83916-01-2
CMF C46 H56 N10 O10

Absolute stereochemistry.

PAGE 1-A



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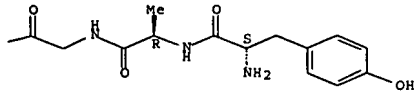


CM 2



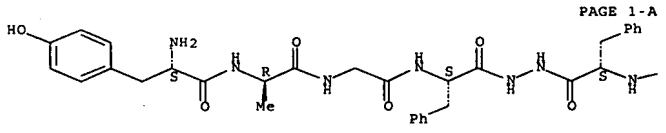


CRN 76-05-1
CMF C2 H F3 O2

L42 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:629505 CAPLUS Full-text
DOCUMENT NUMBER: 107:229505
TITLE: The effect of enkephalin dimers on body temperature in mice
AUTHOR(S): Konecka, Anna Maria; Sroczynska, Irmina; Lipkowski, Andrzej W.
CORPORATE SOURCE: Inst. Genet. Anim. Breed., Pol. Acad. Sci., Jastrzebiec, 05-551, Pol.
SOURCE: Peptides (New York, NY, United States) (1987), 8(3), 431-5
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Short-lasting decreases in rectal temperature in mice were observed after i.p. administration of an enkephalin dimer, Tyr-D-Ala-Gly-Phe-NH-HN-Phe-Gly-D- Ala-Tyr (D-ENK-O), at doses of 0.1, 0.5, 1, 2.5, 5, 10 or 20 mg/kg of body weight Another double-enkephalin Tyr-D-Ala-Gly-Phe-NH-(CH2)3-HN-Phe-Gly-D- Ala-Tyr, failed to produce this effect. The hypothermic effect of D-ENK-O was almost completely reduced by naloxone, suggesting an involvement of opiate receptors in the D-ENK-O produced hypothermia in mice.
IT 83916-01-2
RL: BIOL (Biological study)
(hypothermia induction by, opiate receptor in mediation of)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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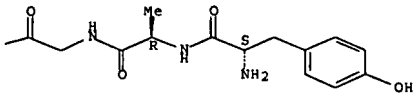


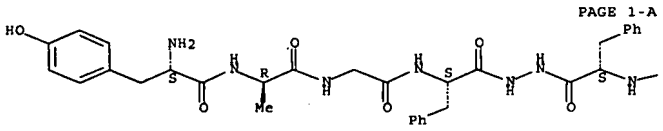
L42 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:452161 CAPLUS Full-text
DOCUMENT NUMBER: 107:52161
TITLE: Bivalent opioid peptide analogs with reduced distances between pharmacophores
AUTHOR(S): Lipkowski, A. W.; Konecka, A. M.; Sroczynska, I.; Przewlocki, R.; Stala, L.; Tam, S. W.
CORPORATE SOURCE: Dep. Med. Chem., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Life Sciences (1987), 40(23), 2283-8
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To investigate the role of distance between 2 opioid peptide pharmacophores on in vitro and in vivo activities, 3 new bivalent opioid analogs [(Try-D-Rhe-NH2)(CH2)n, n = 0-2] were synthesized in which the dipeptide Tyr-D-Phe was connected with diamine moieties ("bridges"). The analog with a hydrazine bridge has high receptor affinity to μ-, κ-, and δ- receptor types, as well as potent and long acting antinociceptive activity after i.p. administration.

IT 83916-01-2
RL: PRP (Properties)
(opioid receptor affinity of)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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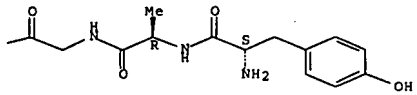






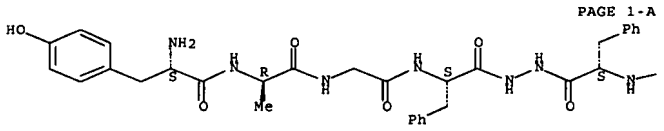
L42 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1984:17851 CAPLUS Full-text
DOCUMENT NUMBER: 100:17851
TITLE: Double opiate peptides. A hypothesis of two different mechanisms of opiate actions
AUTHOR(S): Lipkowski, Andrzej W.; Konopka, Miroslawa; Osipiak, Beata; Gumulka, Witold S.
CORPORATE SOURCE: Dep. Chem., Univ. Warsaw, Warsaw, 02-093, Pol.
SOURCE: Pept., Proc. Eur. Pept. Symp., 17th (1983), Meeting Date 1982, 481-6. Editor(s): Blaha, Karel; Malon, Petr. de Gruyter: Berlin, Fed. Rep. Ger.
CODEN: 50GFAA
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Double opioid peptides of the general formula (Tyr-X-Phe-NH-)2, where X = a single amino acid or a dipeptidyl residue, were synthesized and tested for opioid activity in the guinea pig ileum and mouse vas deferens. The relative agonist or antagonistic activities of these peptides depended on the substitution at X; all peptides containing glycine expressed high agonistic activity in both tests. A hypothesis which relates the structural rigidity of morphine-like compds. and the flexibility of opioid peptides to their interactions with δ and μ receptors is presented. Two different mechanisms of interaction between opioids and δ and μ receptors are proposed.

IT 83916-01-2 88191-65-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(biol. activity of, structure in relation to)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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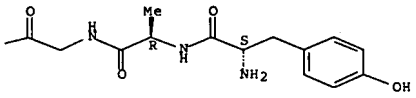
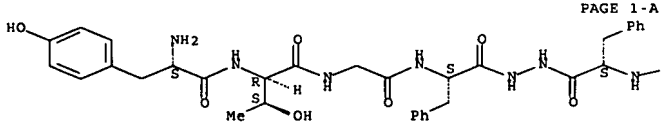


RN 88191-65-5 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-threonylglycyl-, 2-(L-tyrosyl-D-

threonylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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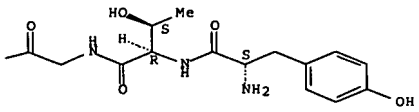
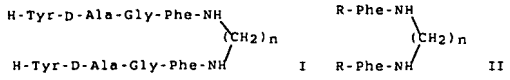


L42 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:17028 CAPLUS Full-text
DOCUMENT NUMBER: 98:17028
TITLE: Double-enkephalins - synthesis, activity on guinea-pig ileum, and analgesic effect
AUTHOR(S): Lipkowski, Andrzej W.; Konecka, Anna Maria; Sroczynska, Irmina
CORPORATE SOURCE: Dep. Chem., Warsaw Univ., Warsaw, 02-093, Pol.
SOURCE: Peptides (New York, NY, United States) (1982), 3(4), 697-700
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB Enkephalin analogs I (n = 0, 3) were prepared by coupling Boc-Tyr-D-Ala-Gly-OH (Boc = Me3CO2C) with phenylalanines II (R = H, n = 0, 3) and Boc-deblocking the resulting protected peptides by HCl/HOAc. Z-Phe-NHNH2 (Z = PhCH2O2C) was treated with Z-Phe-OC6H4NO2-p (III) to give II (R = Z, n = 0), which was Z-deblocked by HBr/HOAc to give II (R = H, n = 0). III was amidated with H2N(CH2)3NH2 to give II (R = Z, n = 3), which was Z-deblocked by HBr/HOAc to give II (R = H, n = 3). I (n = 0) is a potent inhibitor of elec. induced contractions of guinea pig ileum and produces a strong analgesia in mice,



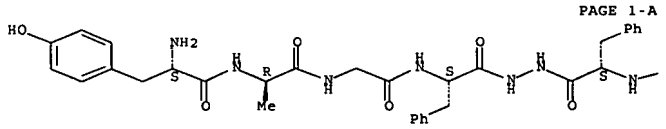


whereas I (n = 3) is less active on the ileum and fails to produce analgesia in mice.

IT 83916-01-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(analgesic activity of)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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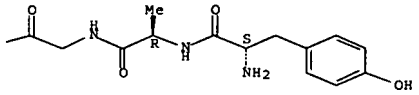
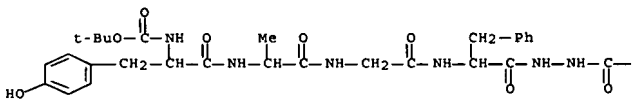


IT 83852-31-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deblocking of)
RN 83852-31-7 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl]-D-alanyl]glycyl]-, 2-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl]-D-alanyl]glycyl]-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

PAGE 1-A



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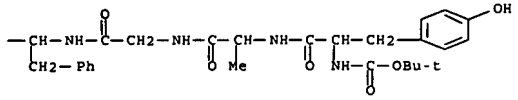
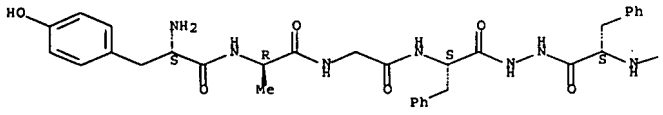


IT 83852-32-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 83852-32-8 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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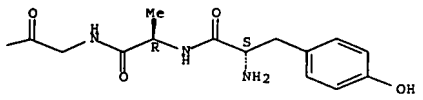
PAGE 1-B







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L12         145 SEA FILE=REGISTRY ABB=ON  L11 AND 8/SQL
L13      734823 SEA FILE=REGISTRY ABB=ON  HYDRAZIDE
L14          90 SEA FILE=REGISTRY ABB=ON  L12 AND L13
L26          57 SEA FILE=REGISTRY ABB=ON  L14 NOT (NORLEU? OR TRICYCLO? OR
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Effective October 17, 2005, revised CAS Information Use Policies apply.
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4233957 PRY<2004
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L46 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:346828 CAPLUS Full-text
DOCUMENT NUMBER: 142:411853
TITLE: Protein-proteophore complexes
INVENTOR(S): Vetter, Dirk; Hersel, Ulrich; Rau, Harald; Schnepf, Robert; Wegge, Thomas
PATENT ASSIGNEE(S): Complex Biosystems G.m.b.H., Germany
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2005034909 | A2 | 20050421 | WO 2004-EP10973 | 20041001 <-- |
| WO 2005034909 | A3 | 20051208 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1525890 | A1 | 20050427 | EP 2003-22097 | 20031002 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| EP 1682186 | A2 | 20060726 | EP 2004-765740 | 20041001 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK | | | | |
| US 2007020224 | A1 | 20070125 | US 2006-574213 | 20061009 <-- |
| PRIORITY APPLN. INFO.: | | | EP 2003-22097 A | 20031002 <-- |
| | | | WO 2004-EP10973 W | 20041001 |





AB The application relates to a composition comprising a water-soluble hyperbranched polymer attached to a core and a biol. active protein. The protein is attached to the core by means of a substantially non-enzymically cleavable linker. The composition is useful for delivering the protein in an unmodified form to its target. A typical macrocycle-protein inclusion complex was manufactured by coupling Fmoc-Cys(S-tBu)-OH, Fmoc-Lys(Fmoc)-OH, 2 units of Fmoc-aminoethyl- and 3-carboxypropyl-terminated polyethylene glycol (d.p. 11) (I), and Fmoc-Cys(Trt)-OH on TGR resin, removing Fmoc, treating the resin with 2/1/1 DMF/Ac2O/C5H5N, reacting the intermediate with a product prepared by reaction of Fmoc-Lys(Mtt)-OH and Fmoc-Lys(Fmoc) with mono-Fmoc-terminated I on TGR resin, removing Fmoc, treating with 3-maleimidopropionic acid (II), and removing the Mtt group, reacting the 2nd intermediate with Ac-Cys-Lys-Cys-NH2, removing the S-tBu groups, reacting the 3rd intermediate with Ac-Dpr(Mal)-Lys-Dpr(Mal)-NH2, reacting the 4th intermediate with II, and reacting the 5th intermediate with the product prepared by reaction of Hb and H2NCONH(CH2)2SS(CH2)2NHCO(CH2)2R (R = maleimido) and cleaving the SS bond.

IT 83916-01-2DP, Biphalin, amino acid-polyethylene glycol derivative complexes
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(water-soluble hyperbranched/macrocyclic polymer proteophore complexes for delivering therapeutically active proteins)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

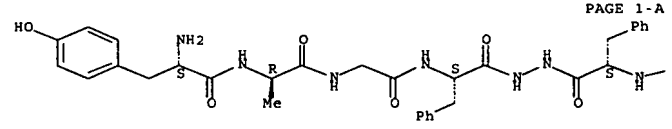
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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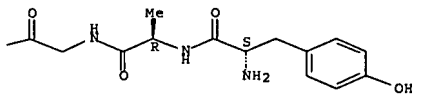


L46 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:678871 CAPLUS Full-text

DOCUMENT NUMBER: 139:214915
TITLE: Hydrolytically-degradable alkylene oxide polymers, preparation, hydrogels, and biological conjugate delivery system
INVENTOR(S): Bentley, Michael D.; Harris, J. Milton; Zhao, Xuan; Battle, William Dudle, III
PATENT ASSIGNEE(S): Nektar Therapeutics Al, Corporation, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003070805 | A1 | 20030828 | WO 2003-US5113 | 20030214 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003213152 | A1 | 20030909 | AU 2003-213152 | 20030214 <-- |
| EP 1476489 | A1 | 20041117 | EP 2003-709198 | 20030214 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2006239961 | A1 | 20061026 | US 2003-371996 | 20030214 <-- |
| PRIORITY APPLN. INFO.: | | | US 2002-357350P P | 20020215 <-- |
| | | | WO 2003-US5113 W | 20030214 <-- |

AB A water-soluble, nonpeptidic polymer comprises ≥2 alkylene oxide-based oligomers linked together by hydrolytically degradable linkages such as carbonates. Typically, the oligomer portion of the polymer is an amphiphilic triblock copolymer having a central propylene oxide block or butylene oxide block positioned between 2 ethylene oxide blocks. The polymer can be hydrolytically degraded into oligomers under physiol. conditions. In aqueous media, the polymer preferably forms thermally-reversible, hydrolytically-degradable hydrogels that can be used for PEGylated drug delivery and related biomedical applications.

IT 83916-01-2DP, Biphalin, conjugate with hydrolytically-degradable alkylene oxide block copolymer
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrolytically-degradable alkylene oxide polymers linked through carbonate groups)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

NTE multichain

SEQ 1 YAGF

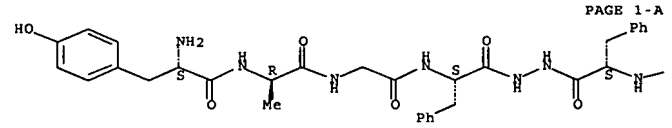
1 YAGF





Absolute stereochemistry.

PAGE 1-A



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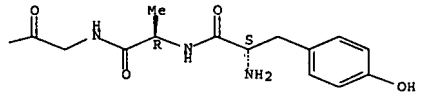


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:551384 CAPLUS Full-text
DOCUMENT NUMBER: 139:117440
TITLE: Preparation of novel piperazinylbenzyl derivatives and method of treating premature ejaculation with these and known delta opioid receptor agonists
INVENTOR(S): Chank, Kwen-jen; King, Klim; Biciunas, Kestutis P.; Mcnutt, Robert W.; Pendergast, William; Jan, Shyi-tai
PATENT ASSIGNEE(S): Ardent Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

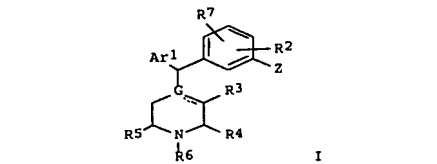
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003057223 | A1 | 20030717 | WO 2003-US87 | 20030102 <-- |
| WO 2003057223 | A9 | 20040429 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003214800 | A1 | 20030724 | AU 2003-214800 | 20030102 <-- |
| US 2003186872 | A1 | 20031002 | US 2003-335764 | 20030102 <-- |
| EP 1469850 | A1 | 20041027 | EP 2003-710631 | 20030102 <-- |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

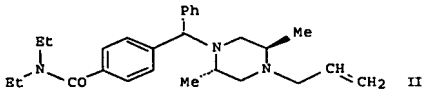
| | | | | | |
|---|---|---|---|---|---|
| NO 2004003240 | A | 20040802 | NO 2004-3240 | | 20040802 <-- |
| US 2007173515 | A1 | 20070726 | US 2007-696806 | | 20070405 <-- |
| PRIORITY APPLN. INFO.: | | | US 2002-345216P | P | 20020102 <-- |
| | | | US 2003-335764 | A1 | 20030102 <-- |
| | | | WO 2003-US87 | W | 20030102 <-- |

OTHER SOURCE(S): MARPAT 139:117440

GI



I



II

AB Compns. and methods for treatment of sexual dysfunctions (particularly premature ejaculation) by administering to a subject a pharmaceutical composition comprising a delta opioid receptor agonist (known compds. such as deltorphin I as well as new piperazinylbenzyl compds. shown as I; variables defined below; e.g. 4-[(αS)-α-((2S,5R)-4-allyl-2,5- dimethyl-1-piperazinyl)benzyl]-N,N-diethylbenzamide (shown as II)) in an amount effective to delay the onset of ejaculation in the subject during sexual stimulation are claimed. Blocking the delta opioid receptor by the selective antagonist naltrindole eliminated the effect of the known delta opioid receptor agonist SNC-80 on ejaculation, indicating that activation of the receptor reduced the electroejaculation in male mice. Binding affinity to delta opioid receptors and EDs and % ejaculation inhibition in mice for some examples of I are tabulated. Although the methods of preparation are not claimed, .apprx.40 example prepns. of I are included. For I: Ar1 is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms C, N, O and S and may include thiophenyl, thiazolyl, furanyl, pyrrolyl, Ph, or pyridyl, and having on a 1st C atom thereof a substituent Y (e.g. H, halo, C1-6 acyl) and on a 2nd ring C thereof a substituent R1 (e.g. H, halo, C1-4 alkyl). Z = H, hydroxy and carboxy and esters thereof; alkoxy, carboxyalkoxy, alkoxycarboxylic acid, hydroxymethyl, and esters thereof; and amino, carboxamides and sulfonamides thereof; G is C or N; R2 is H, halogen, or C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl; R3, R4 and R5 = H and Me, and wherein at least one of R3, R4 or R5 is not H, subject to the proviso that the total number of Me groups does not exceed two, or any two of R3, R4 and R5 together may form a bridge = 1-3 C atoms;. R6 = H, C1-6 alkyl, C2-6 alkenyl, etc.; R7 = H, F; addnl. details are given in the claims; although general structures other than I are claimed, all of the examples appear to fit the I structure.

IT 83916-01-2, Biphalin





RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (preparation of novel piperazinylbenzyl derivs. and method of treating premature ejaculation with these and known delta opioid receptor agonists)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

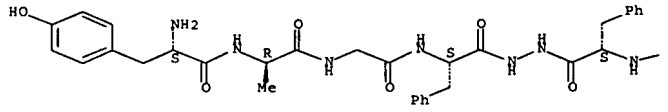
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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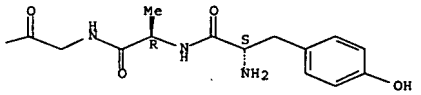


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2003:531299 CAPLUS Full-text |
| DOCUMENT NUMBER: | 140:151789 |
| TITLE: | Conjugation of low molecular weight poly(ethylene glycol) to biphalin enhances antinociceptive profile |
| AUTHOR(S): | Huber, Jason D.; Campos, Chris R.; Egleton, Richard D.; Witt, Ken; Guo, Lihong; Roberts, Michael J.; Bentley, Michael D.; Davis, Thomas P. |
| CORPORATE SOURCE: | Department of Pharmacology, The University of Arizona College of Medicine, Tucson, AZ, 85724, USA |
| SOURCE: | Journal of Pharmaceutical Sciences (2003), 92(7), 1377-1385 CODEN: JPMSAE; ISSN: 0022-3549 |
| PUBLISHER: | Wiley-Liss, Inc. |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |

AB The objectives of this study were to examine the effect of poly(ethylene glycol) (PEG) conjugation on the tyrosine residues of biphalin to determine

the proper size PEG for optimal efficacy and investigate the antinociceptive profile of PEG-biphalin against biphalin via three routes of administration. All antinociception evaluations were made using a radiant-heat tail flick analgesia meter. (2 KDa)2 PEG-biphalin was identified as the optimal size of PEG to enhance the antinociceptive profile following i.v. administration of 685 nmol kg-1 of biphalin or PEG-biphalin [(1 kDa)2, (2 kDa)2, (5 kDa)2, (12 kDa)2, (20 kDa)2]. (2 KDa)2 PEG-biphalin displayed an area under the curve (AUC) .apprx.2.5 times that of biphalin with enhanced analgesia up to 300 min postinjection. (2 KDa)2 PEG-biphalin was equipotent to biphalin following intracerebroventricular administration (0.4 nmol kg-1). Both biphalin and (2 kDa)2 PEG-biphalin were effectively antagonized with naloxone (10 mg kg-1) and a partial antagonistic effect was seen following pretreatment with naltrindole (20 mg kg-1). (2 KDa)2 PEG-biphalin showed significantly increased potency (A50) when administered i.v. and s.c. Addnl., (2 kDa)2 PEG-biphalin demonstrated a significantly enhanced antinociceptive profile (AUC) via all routes of administration tested. These findings indicate that PEG conjugation to biphalin retains opioid-mediated effects observed with biphalin and is a valuable tool for eliciting potent, sustained analgesia via parenteral routes of administration.

IT 83916-01-2DP, Biphalin, conjugates with polyethylene glycols
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugation of low mol. weight poly(ethylene glycol) to biphalin enhances antinociceptive profile)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

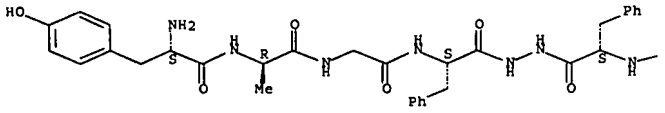
NTE multichain

SEQ 1 YAGF

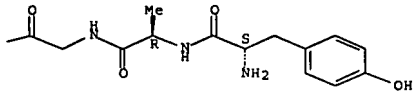
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B







IT 83916-01-2, Biphalin
RL: PKT (Pharmacokinetics); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(conjugation of low mol. weight poly(ethylene glycol) to biphalin enhances antinociceptive profile)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

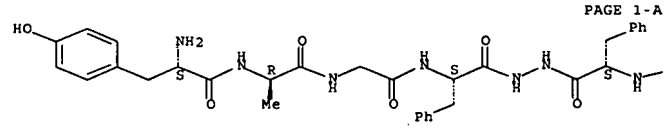
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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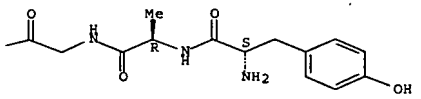


REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2002:834418 CAPLUS Full-text |
| DOCUMENT NUMBER: | 138:331601 |
| TITLE: | Pluronic P85 block copolymer enhances opioid peptide analgesia |
| AUTHOR(S): | Witt, Ken A.; Huber, Jason D.; Egleton, Richard D.; Davis, Thomas P. |
| CORPORATE SOURCE: | Department of Pharmacology, College of Medicine, The University of Arizona, Tucson, AZ, USA |
| SOURCE: | Journal of Pharmacology and Experimental Therapeutics (2002), 303(2), 760-767<br>CODEN: JPETAB; ISSN: 0022-3565 |
| PUBLISHER: | American Society for Pharmacology and Experimental Therapeutics |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |

AB Peptide-based drug development is a rapidly growing field within pharmaceutical research. Nevertheless, peptides have found limited clin. use due to several physiol. and pathol. factors. Pluronic block copolymers represent a growing technol. with the potential to enhance efficacy of peptide therapeutics. This investigation assesses Pluronic P85 (P85) and its potential to enhance opioid peptide analgesia. Two opioid peptides, [D-Pen2,D-Pen5]-enkephalin (DPDPE) and biphalin, were examined as to the benefits of P85 coadministration, above (1.0%) and below (0.01%) the critical micelle concentration, with morphine as a nonpeptide control. P85 was examined in vitro to assess blood-brain barrier uptake in association with P-glycoprotein effect, DPDPE and morphine being P-glycoprotein substrates. P85 coadministration with DPDPE and biphalin showed increased ($p < 0.01$) analgesia with both 0.01 and 1.0% P85. Morphine showed increased ($p < 0.01$) analgesia with 0.01% P85 only. This increase in analgesia is due to both an increase in peak effect, as well as a prolongation of effect. P85 increased cellular uptake of 125I-DPDPE and [3H]morphine at 0.01% ($p < 0.01$) and 1.0% ($p < 0.01$ and $p < 0.05$, resp.). Cyclosporin-A coadministration with 125I-DPDPE and [3H]morphine increased cellular uptake ($p < 0.01$ and $p < 0.05$, resp.). 125I-DPDPE and [3H]morphine coadministered with 0.01% P85 and cyclosporin-A increased cellular uptake compared with control ($p < 0.01$) and compared with cyclosporin-A coadministration without P85 ($p < 0.01$ and $p < 0.05$, resp.). This indicates that, in addition to P-gp inhibition, 0.01% P85 increased 125I-DPDPE and [3H]morphine uptake. In our examination, we determined that P85 enhanced the analgesic profile of biphalin, DPDPE, and morphine, both above and below the critical micelle concentration

IT 83916-01-2, Biphalin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pluronic P85 block copolymer enhances opioid peptide analgesia)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

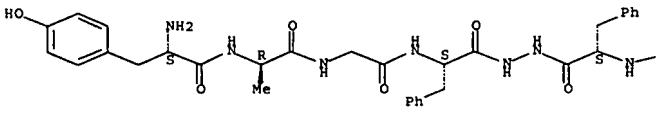
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

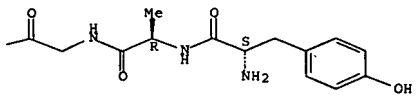
PAGE 1-A







PAGE 1-B



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:431553 CAPLUS Full-text
DOCUMENT NUMBER: 138:49590
TITLE: Immunomodulation by biphalin, dimeric synthetic opioid peptide, and its analog
AUTHOR(S): Mehrotra, S.; Prajapati, R. K.; Haq, W.; Singh, V. K.
CORPORATE SOURCE: Department of Immunology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, 226 014, India
SOURCE: Immunopharmacology and Immunotoxicology (2002), 24(1), 83-96
CODEN: IITOEF; ISSN: 0892-3973
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The opioid pentapeptides called enkephalins were originally described as the endogenous ligands for the opioid receptors. Although their precise physiol. significance still remains elusive, the enkephalins have been reported to exhibit analgesic, antidepressant, antianxiety and anticonvulsant activities. In addition, enkephalins have also been shown to act as immunomodulator. The first generation of dimeric peptides was derived from enkephalins. Biphalin [(Tyr-D-Ala-Gly-Phe-NH)2] is a bivalent opioid analog containing two tyrosine residues. We have evaluated the immunomodulatory properties of biphalin and its analogs in various in vitro tests. We report that biphalin and one of its analogs [Tyr-D-Ala-Gly-Phe-NH,NH-Phe(p-Cl)-H] stimulate human T cell proliferation, natural killer (NK) cell cytotoxicity in vitro and interleukin-2 (IL-2) production Biphalin and its analog also released chemokine like factor in the culture supernatant that was responsible for increased chemotaxis of monocytes. Furthermore, these peptides inhibited tumor necrosis factor (TNF-α) production in lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells (PBMC) and nitric oxide (NO). Production in mouse macrophage cells, RAW 264.7. Our observations suggest immunomodulatory property of biphalin and its analog.

IT 83916-01-2P, Biphalin 479485-63-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(immunomodulation by biphalin, dimeric synthetic opioid peptide, and its analog)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

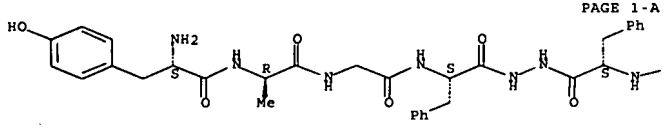
NTE multichain

SEQ 1 YAGF

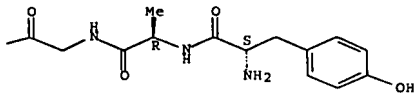
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RN 479485-63-7 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-β-methyl-, 2-(L-tyrosyl-D-alanylglycyl-β-methyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

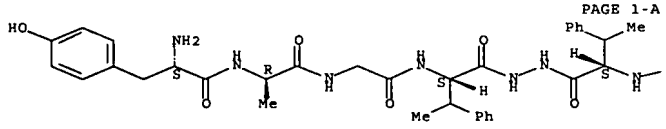
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

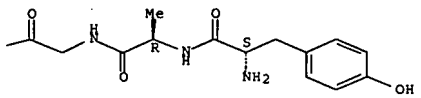
PAGE 1-A







PAGE 1-B



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:353321 CAPLUS Full-text
DOCUMENT NUMBER: 136:359644
TITLE: Compositions for enhanced delivery of bioactive molecules
INVENTOR(S): Lewis, Danny; Schmidt, Paul; Hinds, Kenneth
PATENT ASSIGNEE(S): PR Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002036169 | A2 | 20020510 | WO 2001-US45154 | 20011031 <-- |
| WO 2002036169 | A3 | 20030731 | | |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002020002 | A5 | 20020515 | AU 2002-20002 | 20011031 <-- |
| US 2002155158 | A1 | 20021024 | US 2001-999820 | 20011031 <-- |
| US 6706289 | B2 | 20040316 | | |
| EP 1353701 | A2 | 20031022 | EP 2001-992587 | 20011031 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| CN 1507357 | A | 20040623 | CN 2001-821388 | 20011031 <-- |
| JP 2004534721 | T | 20041118 | JP 2002-538978 | 20011031 <-- |
| US 2004185103 | A1 | 20040923 | US 2004-766106 | 20040127 <-- |
| PRIORITY APPLN. INFO.: | | | US 2000-244499P | P 20001031 <-- |
| | | | US 2001-999820 | A1 20011031 <-- |
| | | | WO 2001-US45154 | W 20011031 <-- |

AB Formulations for controlled, prolonged release of bioactive mols. such as therapeutic proteins, peptides and oligonucleotides have been developed. These formulations are based on solid microparticles or nanoparticles formed of the combination of biodegradable, synthetic polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and copolymers. Bioactive mols. are coupled to hydrophilic polymers such as polyethylene glycol or polypropylene glycol

and formulated to provide controlled release. The bioactive mols. are more stable, less immunogenic and have improved release rate profiles with lower burst levels and increased drug loading relative to the same bioactive mols. lacking coupled hydrophilic polymers. The controlled release formulations can be administered by injection, by inhalation, nasally, or orally. Leu-enkephalin was covalently modified with polyethylene glycol. The peptide was converted to its PEG-modified form. PEG-leu-enkephalin was dissolved in a 1:9 DMSO:PBS mixture to a final concentration of 50 mg/mL. PLGA was dissolved in methylene chloride to a final concentration of 200 mg/mL. The primary emulsion was created by homogenizing 200 µL of the peptide solution with 3 mL of the polymer solution at 10,000 rpm for 3 min. After the solvent had evaporated and the microparticles had hardened, they were collected by filtration and dried in vacuo before anal. The particles were characterized for core loading encapsulation efficiency, and particle size. Covalent coupling of PEG 5000 to leu-enkephalin increased the drug loading attainable from 0.07 to 0.36 % for the double emulsion technique and from 0.3 to 3.95 % for the monophase method.

IT 83916-01-2D, Biphalin, polymer conjugates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for enhanced delivery of bioactive mols.)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

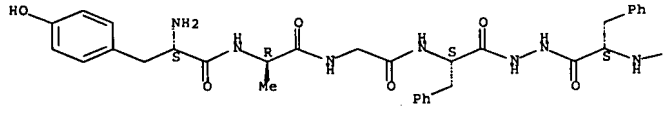
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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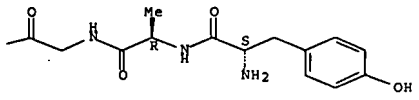


L46 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:350616 CAPLUS Full-text
DOCUMENT NUMBER: 138:112319
TITLE: PEG biphalin: a potent long-acting analgesic





AUTHOR(S): Bentley, M.; Davis, T.; Egelton, R.; Guo, L.; Huber, J.; Roberts, M.; Witt, K.
CORPORATE SOURCE: Shearwater Corporation, Huntsville, AL, 35801, USA
SOURCE: Proceedings - 28th International Symposium on Controlled Release of Bioactive Materials and 4th Consumer & Diversified Products Conference, San Diego, CA, United States, June 23-27, 2001 (2001), Volume 2, 1287-1288. Controlled Release Society: Minneapolis, Minn.
CODEN: 69CNY8
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Polyethylene glycol derivs. of the enkephalin dimer, biphalin, were prepared The derivs. were potent, long-acting analgesics in both mice and rats and can be delivered i.v., s.c., or i.m. Antagonist studies revealed that PEG-biphalin is a µ/δ-agonist.

IT 83916-01-2DP, Biphalin, PEG conjugates
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of PEG-biphalin as potent long-acting analgesic)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

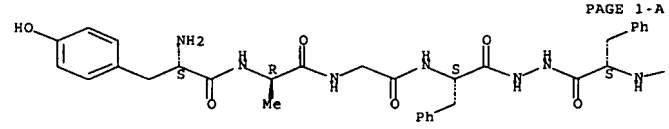
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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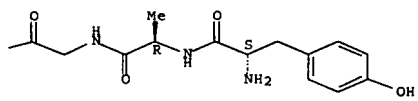


IT 83916-01-2, Biphalin
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation of PEG-biphalin as potent long-acting analgesic)

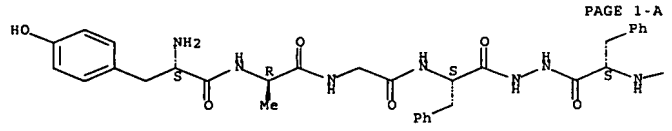
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

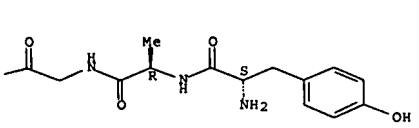
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.




REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:918512 CAPLUS Full-text
DOCUMENT NUMBER: 136:226920
TITLE: Interaction of enkephalin peptides with anionic model membranes
AUTHOR(S): Romanowski, Marek; Zhu, Xiaoyun; Kim, Kathy; Hruby, Victor J.; O'Brien, David F.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Biochimica et Biophysica Acta, Biomembranes ( 2002), 1558(1), 45-53
CODEN: BBBMBS; ISSN: 0005-2736
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB According to the model for passive transport across the membranes, the total flow of permeant mols. is related to the product of the water-membrane partition coefficient and the diffusion coefficient, and to the water-membrane interfacial barrier. The effect of membrane surface charge on the permeability and interaction of analgesic peptide ligands with model membranes was investigated. A mixture of zwitterionic phospholipids with cholesterol was used as a model membrane. The lipid membrane charge d. was controlled by





the addition of anionic 1-palmitoyl-2- oleoylphosphatidylserine. Two classes of highly potent analgesic peptides were studied, c[D-Pen2,D-Pen5]enkephalin (DPDPE) and biphalin, a dimeric analog of enkephalin. The effect of increased surface charge on the permeability of the zwitterionic DPDPE is a relatively modest decrease, that appears to be due to a diminished partition coefficient On the other hand the binding of the dicationic biphalin ligands to membranes increases proportionally with increased neg. surface charge. This effect translates into a significant reduction of biphalin permeability by reducing the diffusion of the peptide across the bilayer. These expts. show the importance of electrostatic effects on the peptide-membrane interactions and suggest that the neg. charge naturally present in cell membranes may hamper the membrane transport of some peptide drugs, especially cationic ones, unless there are cationic transporters present.

IT 83916-01-2, Biphalin 402950-63-4
RL: PEP (Physical, engineering or chemical process); PKT (Pharmacokinetics); PRP (Properties); PYP (Physical process); BIOL (Biological study); PROC (Process)
(interaction of enkephalin peptides with anionic model membranes)

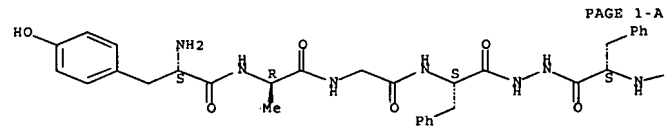
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

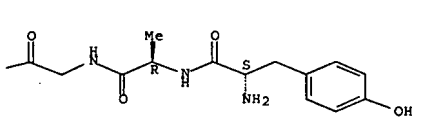
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.




RN 402950-63-4 CAPLUS
CN L-Phenylalanine, L-tyrosyl-L-alanylglycyl-β-methyl-, 2-[L-tyrosyl-L-alanylglycyl-(βR)-β-methyl-L-phenylalanyl]hydrazide, (βR)- (9CI) (CA INDEX NAME)

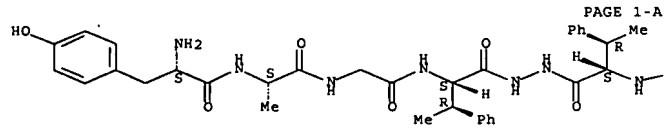
NTE multichain

modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.



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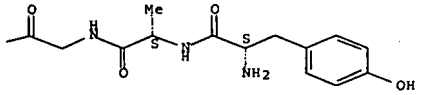
PAGE 1-B



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L46 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:311684 CAPLUS Full-text
DOCUMENT NUMBER: 135:46430
TITLE: Application of 4-alkoxy-2-hydroxybenzaldehyde (AHB) linker to solid phase synthesis of biphalin; dimeric peptide connected at C-termini through hydrazine
AUTHOR(S): Okayama, Toru; Hruby, Victor J.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Peptide Science (2001), Volume Date 2000, 37th, 35-38
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Japanese Peptide Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A symposium report. The authors recently reported on a 4-alkoxy-2-hydroxybenzaldehyde (AHB) linker that is applicable to both Fmoc and Boc chemical by switching the acid stability through an "on-and-off" of the O-acyl group on the phenolic hydroxyl group in the linker. In the present study, the first successful synthesis of biphalin on a solid support is described. Using two different resin-bound hydrazines, both stepwise and simultaneous elongation reactions were examined and the former afforded the desired biphalin in high yield, while the latter gave considerable amts. of byproducts.
IT 83916-01-2P, Biphalin
RL: SPN (Synthetic preparation); PREP (Preparation)





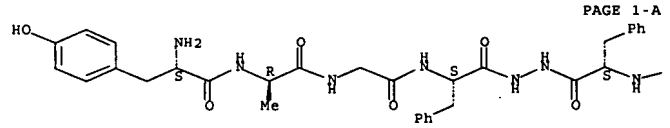
(solid-phase synthesis of biphalin using (alkoxy)hydroxybenzaldehyde linker and solid-supported hydrazine for building the peptide chain)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

NTE multichain

SEQ 1 YAGF

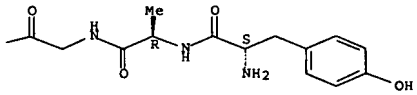
1 YAGF

Absolute stereochemistry.



PAGE 1-A

PAGE 1-B



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:265280 CAPLUS Full-text
DOCUMENT NUMBER: 134:271292
TITLE: Polymer-stabilized neuropeptides
INVENTOR(S): Bentley, Michael David; Roberts, Michael James
PATENT ASSIGNEE(S): Shearwater Polymers, Inc., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001024831 | A2 | 20010412 | WO 2000-US41070 | 20001004 <-- |
| WO 2001024831 | A3 | 20020307 | | |
| WO 2001024831 | A9 | 20021114 | | |

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HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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| CA 2385533 | A1 | 20010412 | CA 2000-2385533 | 20001004 <-- |
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| MX 2002PA03176 | A | 20020930 | MX 2002-PA3176 | 20020326 <-- |
| US 2003139346 | A1 | 20030724 | US 2003-354879 | 20030130 <-- |
| US 2003144207 | A1 | 20030731 | US 2003-354683 | 20030130 <-- |
| US 2004038899 | A1 | 20040226 | US 2003-647561 | 20030825 <-- |

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| PRIORITY APPLN. INFO.: | US 1999-157503P | P | 19991004 <-- |
| | US 1999-166589P | P | 19991119 <-- |
| | US 2000-678997 | A3 | 20001004 <-- |
| | WO 2000-US41070 | W | 20001004 <-- |
| | US 2001-956271 | A3 | 20010919 <-- |
| | US 2001-956440 | A1 | 20010919 <-- |

AB A substantially hydrophilic conjugate is provided having a peptide that is capable of passing the blood-brain barrier covalently linked to a water-soluble nonpeptidic polymer such as polyethylene glycol. The conjugate exhibits improved solubility and in vivo stability and is capable of passing the blood-brain barrier of an animal. For example, i.v. administration of dipegylated biphalin [(methoxypolyethylene glycol 2000)2-biphalin] gave a longer lasting analgesic effect in rats than native biphalin at the various doses tested. Rats given dipegylated biphalin by s.c. or i.m. administration showed elevated and sustained levels of analgesic activity as compared to native biphalin at the same concentration

IT 83916-01-2D, Biphalin, polymer conjugates
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymer-stabilized analgesic neuropeptides for passing blood-brain barrier)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

NTE multichain

SEQ 1 YAGF

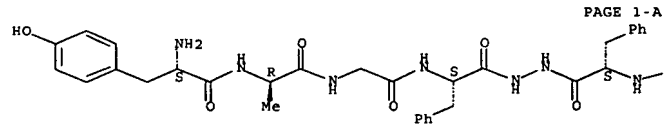
1 YAGF

Absolute stereochemistry.





PAGE 1-A



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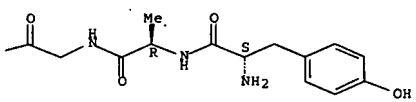


IT 83916-01-2, Biphalin
RL: RCT (Reactant); RACT (Reactant or reagent)
(polymer-stabilized analgesic neuropeptides for passing blood-brain barrier)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

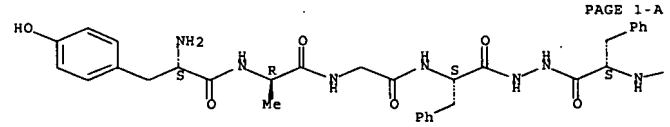
NTE multichain

SEQ 1 YAGF

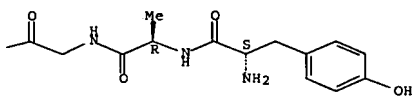
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L46 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:128958 CAPLUS Full-text
DOCUMENT NUMBER: 134:315943
TITLE: Characterization and analysis of biphalin: an opioid peptide with a palindromic sequence
AUTHOR(S): Hettiarachchi, K.; Ridge, S.; Thomas, D. W.; Olson, L.; Obi, C. R.; Singh, D.
CORPORATE SOURCE: SRI International, Menlo Park, CA, 94025, USA
SOURCE: Journal of Peptide Research (2001), 57(2), 151-161
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Among the many opioid peptides developed to date as nonaddictive analgesics, biphalin has exhibited extraordinary high potency and many other desirable characteristics. Biphalin is an octapeptide consisting of two monomers of a modified enkephalin, attached via a hydrazine bridge, and with the amino acids assembled in a palindromic sequence. Its structure is (Tyr-D-Ala-Gly-Phe-NH-)-2. However, this unique peptide, like any other synthetic peptide, needs strict quality control because of certain drawbacks associated with peptide synthesis. This paper discusses our approaches to characterizing and analyzing biphalin. Many techniques were used, including elemental anal., amino acid anal., amino acid sequence anal. (AASA), mass spectrometry (MS), 1H-NMR, 1H-correlated spectroscopy (COSY)-NMR, high-performance liquid chromatog. (HPLC) and capillary electrophoresis (CE). Electrospray ionization (ESI) mass spectrometry, which included both ESI-MS and ESI-MS/MS, was performed to confirm the full sequence because AASA results alone verified only the monomer sequence, and not the full sequence. Although the 1H-NMR results led to a preliminary assignment of many protons, the 1H COSY-NMR results allowed for unequivocal assignment of almost all protons. Peptide purity was determined using two techniques, reversed-phase HPLC and CE. The counter-ion of the peptide, trifluoroacetic acid, was determined by CE, using an indirect detection method developed previously in our laboratory This paper illustrates successful application of nonconventional techniques to characterize and analyze a structurally modified peptide, biphalin, when standard techniques for peptide anal. are inadequate.

IT 83916-01-2, Biphalin
RL: PRP (Properties)
(characterization and anal. of biphalin)

RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

NTE multichain

SEQ 1 YAGF

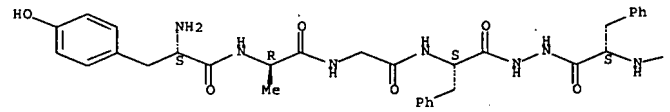
1 YAGF

Absolute stereochemistry.

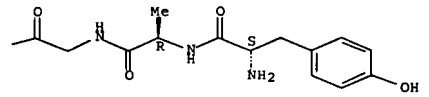




PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:627979 CAPLUS Full-text
DOCUMENT NUMBER: 133:203014
TITLE: Method and composition for treating irritable bowel syndrome using low doses of opioid receptor antagonists
INVENTOR(S): Crain, Stanley M.; Shen, Ke-fei; Fleischner, Gerald M.
PATENT ASSIGNEE(S): Albert Einstein College of Medicine of Yeshiva University, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000051592 | A1 | 20000908 | WO 2000-US5473 | 20000302 <-- |
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| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6194382 | B1 | 20010227 | US 1999-261361 | 19990303 <-- |
| CA 2365391 | A1 | 20000908 | CA 2000-2365391 | 20000302 <-- |
| EP 1156792 | A1 | 20011128 | EP 2000-915994 | 20000302 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2002538111 | T | 20021112 | JP 2000-602060 | 20000302 <-- |
| AU 780013 | B2 | 20050224 | AU 2000-37170 | 20000302 <-- |
| US 2001018413 | A1 | 20010830 | US 2001-754840 | 20010104 <-- |

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|---|---|---|---|---|---|
| US 6395705 | B2 | 20020528 | | | |
| US 2002173466 | A1 | 20021121 | US 2002-114909 | 20020403 | <-- |
| US 6737400 | B2 | 20040518 | | | |
| US 2005101622 | A1 | 20050512 | US 2004-807508 | 20040323 | <-- |
| AU 2005202245 | A1 | 20050616 | AU 2005-202245 | 20050524 | <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-261361 A | 19990303 | <-- |
| | | | WO 2000-US5473 W | 20000302 | <-- |
| | | | US 2001-754840 A1 | 20010104 | <-- |
| | | | US 2002-114909 A1 | 20020403 | <-- |

AB This invention relates to a method for treating a subject with irritable bowel syndrome ("IBS") which comprises long-term administration of an opioid receptor antagonist at an appropriately low dose which will selectively antagonize excitatory opioid receptor functions, but not inhibitory opioid receptor functions, in myenteric neurons in the intestinal tract as well as in neurons of the central nervous system ("CNS"). The administration of the opioid receptor antagonist at a low dose enhances the potency of the inhibitory effects of endogenous opioid peptides present in the intestinal tract and the CNS, thereby reducing abdominal pain and stool frequency resulting from abnormally supersensitized excitatory opioid receptor functions. The invention also relates to a composition for treating a subject with IBS, which comprises an ED of an opioid receptor antagonist, and a pharmaceutically acceptable carrier. Patients with IBS were treated orally with low doses of naltrexone.

IT 83916-01-2, Biphalin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method and composition for treating irritable bowel syndrome using low doses of opioid receptor antagonists)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

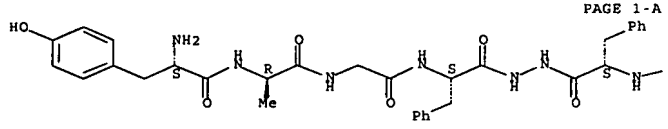
NTE multichain

SEQ 1 YAGF

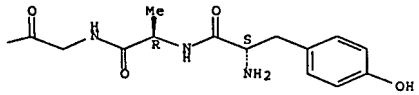
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B







REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:720292 CAPLUS Full-text
DOCUMENT NUMBER: 130:61238
TITLE: The relationship between structure and activity among opioid peptides
AUTHOR(S): Deschamps, Jeffrey R.; George, Clifford; Flippen-Anderson, Judith L.
CORPORATE SOURCE: Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC, 20375, USA
SOURCE: Letters in Peptide Science (1998), 5(5-6), 337-340
CODEN: LPSCEM; ISSN: 0929-5666
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Since the discovery and isolation of the endogenous opioid peptides Leu- and Met-enkephalin, structural studies have been focused on deducing the bioactive conformation of the peptide ligands. Theor., linear peptides can have many different backbone conformations, yet early x-ray studies on enkephalin and its analogs showed only two different backbone conformations: extended and single β-bend. More recent reports include a third conformation for Leu-enkephalin and constrained opioid peptides from two "new" classes (i.e. cyclic and "all-aromatic" peptides). In this report the relationship between solid-state x-ray structure and opioid peptide activity is examined The N-terminal amine nitrogen and the two aromatic rings have previously been identified as structural features important to the biol. activity of opioid peptides. From x-ray studies we find that the distances between the centroids of the aromatic rings, and between the N-terminal amino nitrogen and the centroid of the phenylalanine ring, vary over a large range. There is a discernible relationship, however, between the separation of the two rings and their orientation that correlates with activity.

IT 83916-01-2, Biphalin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(relationship between structure and activity among opioid peptides)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

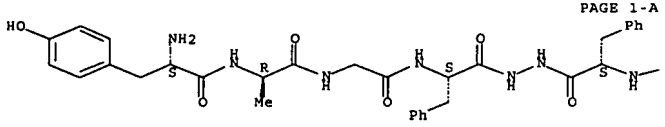
NTE multichain

SEQ 1 YAGF

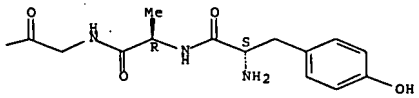
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:532141 CAPLUS Full-text
DOCUMENT NUMBER: 129:255248
TITLE: Transport of Opioid Peptides into the Central Nervous System
AUTHOR(S): Egleton, Richard D.; Abbruscato, Thomas J.; Thomas, Sarah A.; Davis, Thomas P.
CORPORATE SOURCE: Department of Pharmacology College of Medicine, University of Arizona, Tucson, AZ, 85724., USA
SOURCE: Journal of Pharmaceutical Sciences (1998), 87(11), 1433-1439
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peptide hormones and neurotransmitters play crucial roles in the maintenance of physiol. function at both the cellular and organ level. Although peptide neuropharmaceuticals have enormous potential in the treatment of disease states, the blood-brain barrier (BBB) generally prevents the entry of peptides into the brain either by enzyme degradation or by specific properties of the BBB. Peptides that act at opioid receptors are currently being designed for analgesia and to reduce the unwanted side effects associated with morphine, such as addiction and inhibition of gastric motility. It has been the focus of our group to produce stable peptide analogs of Met-enkephalin, that lead to analgesia without side effects. In this paper we present the methodologies that have been used to elucidate the transport mechanisms of three peptides across the BBB. By using a primary endothelial cell culture model of the BBB, in situ perfusion, and kinetic anal., we show that D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen- Thr-NH2 crosses the BBB via diffusion, [D-penicillamine2,5]enkephalin uses a combination of diffusion and a saturable transport mechanism, and biphalin ([Tyr-D-Ala-Gly-Phe-NH]2) uses diffusion and the large neutral amino acid carrier. Understanding BBB transport mechanisms for peptides will aid in the rational design of peptides targeted to the brain.
IT 83916-01-2, Biphalin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL





(Biological study); PROC (Process)
(opioid peptide transport into central nervous system and mechanisms therefor)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

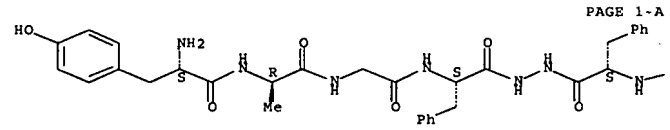
NTE multichain

SEQ 1 YAGF

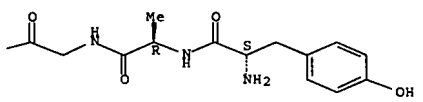
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:564280 CAPLUS Full-text
DOCUMENT NUMBER: 127:229838
TITLE: Brain and spinal cord distribution of biphalin: correlation with opioid receptor density and mechanism of CNS entry
AUTHOR(S): Abbruscato, Thomas J.; Thomas, Sarah A.; Hruby, Victor J.; Davis, Thomas P.
CORPORATE SOURCE: Departments of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, 85724, USA
SOURCE: Journal of Neurochemistry (1997), 69(3), 1236-1245
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Biphalin [(Tyr-D-Ala-Gly-Phe-NH)2] is a bivalent, opioid peptide containing two pharmacophores linked by a hydrazine bridge. When administered intracerebroventricularly, it has been shown to be more potent than morphine

and etorphine at eliciting antinociception. Biphalin has also been shown to cross both the blood-brain and blood-cerebrospinal fluid barriers. To understand the basis of biphalin's potency, regional brain and spinal cord distribution studies with [125I-Tyr1]biphalin were performed 5, 20, and 40 min after i.v. bolus injections. A statistically greater amount of [125I-Tyr1]biphalin was detected in the nucleus accumbens compared with other brain regions. This correlates with the high d. of δ- and μ-opioid receptor mRNA and binding sites shown to be expressed in the nucleus accumbens. Also, a statistically greater amount of [125I-Tyr1]biphalin was detected in two other circumventricular organs, the choroid plexus and pituitary, when compared with other brain regions. These studies provide evidence that biphalin can reach not only brain sites, but also spinal sites to elicit antinociception. The overall CNS distribution of [125I-Tyr1]biphalin was decreased with naloxone, D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2, or naltrindole pretreatment, showing that biphalin detected in the brain and spinal cord is binding to δ- and μ-opioid receptors. Addnl. in situ brain perfusion expts. identified a saturable component contributing to CNS entry of [125I-Tyr1]biphalin, which could be described by Michaelis-Menten kinetics with a Km of 2.6 μM, Vmax of 14.6 pmol/min/g, and Kd of 0.568 μL/min/g. Brain entry of [125I-Tyr1]biphalin was sensitive to 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid and L-phenylalanine, suggesting use of the large neutral amino acid carrier. This work provides evidence that biphalin is a promising, potent analgesic that has a unique mechanism for reaching both spinal and supraspinal opioid receptor sites.

IT 83916-01-2, Biphalin
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(brain and spinal cord distribution of biphalin and correlation with opioid receptor d. and mechanism of CNS entry)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

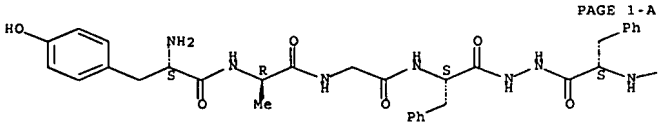
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A





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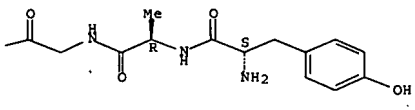



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:696061 CAPLUS Full-text
DOCUMENT NUMBER: 126:26946
TITLE: Structure-activity relationships and synthetic study for biphalin-1,1'-stereochemical and truncation modifications
AUTHOR(S): Li, G.; Haq, W.; Xiang, L.; De Leon, A.; Davis, P.; Hughes, R.; Lou, B.; Gillespie, T. J.; Porreca, F.; et al.
CORPORATE SOURCE: Department Chemistry, University Arizona, Tucson, AZ, 85721, USA
SOURCE: Peptides: Chemistry, Structure and Biology, Proceedings of the American Peptide Symposium, 14th, Columbus, Ohio, June 18-23, 1995 (1996), Meeting Date 1995, 699-700. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Mayflower Scientific: Kingswinford, UK.
CODEN: 63NTAF
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The opioid receptor binding affinities and selectivities of a series of biphalin analogs were determined and correlated with structure.

IT 83916-01-2, Biphalin 184581-21-3 184758-92-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structure-activity relationships and synthetic study for biphalin-1,1'-stereochem. and truncation modifications)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

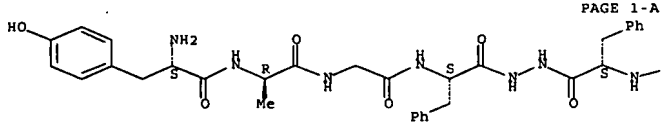
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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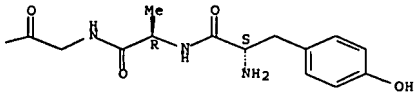


RN 184581-21-3 CAPLUS

CN L-Phenylalanine, (βS)-β,2-dimethyl-L-tyrosyl-D-alanylglycyl-, 2-[(βS)-β,2-dimethyl-L-tyrosyl-D-alanylglycyl-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

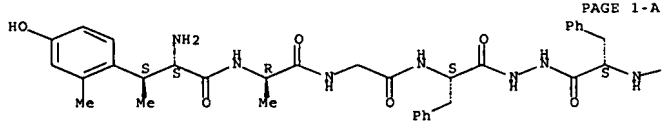
NTE multichain
modified

SEQ 1 YAGF

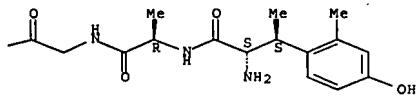
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RN 184758-92-7 CAPLUS





CN L-Phenylalanine, (βR)-β,2-dimethyl-D-tyrosyl-D-alanylglycyl-, 2-[(βR)-β,2-dimethyl-D-tyrosyl-D-alanylglycyl-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

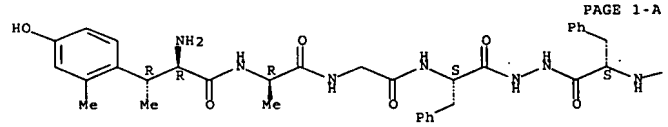
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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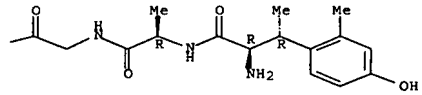


L46 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:961742 CAPLUS Full-text

DOCUMENT NUMBER: 124:1154

TITLE: Biphalin, an enkephalin analog with unexpectedly high antinociceptive potency and low dependence liability in vivo, selectively antagonizes excitatory opioid receptor functions of sensory neurons in culture

AUTHOR(S): Shen, Ke-Fei; Crain, Stanley M.

CORPORATE SOURCE: Department of Neuroscience, Albert Einstein College of Medicine, Yeshiva University, 1300 Morris Park Avenue, Bronx, NY, 10461, USA

SOURCE: Brain Research (1995), 701(1,2), 158-66
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mechanism of action of the dimeric enkephalin peptide, biphalin (Tyr-D-Ala-Gly-Phe-NH2)2, which was previously shown to have remarkable high antinociceptive potency and low dependence liability in vivo, has now been studied by electrophysiol. analyses of its effects on the action potential duration (APD) of nociceptive types of sensory dorsal root ganglion (DRG) neurons in culture. Acute application of biphalin (pM-μM) elicited only dose-

dependent, naloxone-reversible inhibitory (APD-shortening) effects on DRG neurons. Furthermore, at pM concns. that evoked little or no alteration of the APD of DRG neurons biphalin selectively antagonized excitatory (APD-prolonging) effects of low (fM-nM) concns. of bimodally-acting μ and δ opioid agonists and unmasked potent inhibitory effects of these opioids. This dual opioid inhibitory-agonist/excitatory-antagonist property of biphalin is remarkably similar to that previously observed in studies of the ultra-potent opioid analgesic, etorphine on DRG neurons and in sharp contrast to the excitatory agonist action of most μ, δ and κ opioid alkaloids and peptides when tested at low (pM-nM) concns. Chronic treatment of DRG neurons with high (μM) concns. of biphalin did not result in supersensitivity to the excitatory effects of naloxone nor in tolerance to opioid inhibition effects, in contrast to the excitatory opioid supersensitivity and tolerance that develop in chronic morphine- or DADLE-treated, but not chronic etorphine-treated, neurons. These studies on DRG neurons in vitro may help to account for the unexpectedly high antinociceptive potency and low dependence liability of biphalin as well as etorphine in vivo.

IT 83916-01-2, Biphalin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antagonizes excitatory opioid receptor functions of sensory neurons in culture)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

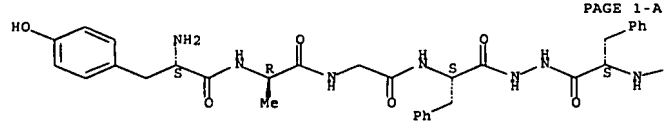
NTE multichain

SEQ 1 YAGF

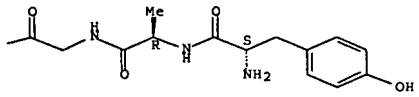
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L46 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN





ACCESSION NUMBER: 1993:509418 CAPLUS Full-text
DOCUMENT NUMBER: 119:109418
TITLE: Antinociceptive profile of biphalin, a dimeric enkephalin analog
AUTHOR(S): Horan, Peter J.; Mattia, Antonia; Bilsky, Edward J.; Weber, Steven; Davis, Thomas P.; Yamamura, Henry I.; Malatynska, Ewa; Appleyard, Suzanne M.; Slaninova, Jirina; et al.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Arizona, Tucson, AZ, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 265(3), 1446-54
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The dimeric enkephalin biphalin (Tyr-D-Ala-Gly-Phe-NH)2 was evaluated in mice using antinociceptive, gastrointestinal and phys. dependence paradigms and compared with that of morphine (reference μ agonist) and etorphine (ultrapotent opioid agonist). Intracerebroventricular biphalin was 6.7- and 257-fold more potent than etorphine or morphine in eliciting antinociception. When administered i.t., biphalin produced only a 60% maximal antinociceptive effect in the tail-flick test even when given at doses up to 3 orders of magnitude higher than those effective i.c.v.; morphine was equipotent in this assay when given i.c.v. or i.t. Both morphine and biphalin were equipotent after i.p. administration. In spite of its antinociceptive effectiveness after i.p. administration, only a small fraction of [125I]biphalin penetrated to the brain (0.051%, at 20 min). After i.c.v. administration, biphalin antinociception was antagonized by receptor selective doses of β-funaltrexamine (μ antagonist), naloxonazine (μ1 antagonist), ICI 174,864 (δ antagonist) and [D-Ala2,Cys4]deltorphin (δ2 antagonist), but not by [D-Ala2,Leu5,Cys6]enkephalin (δ1 antagonist) or nor-binaltorphimine (κ antagonist), whereas etorphine antinociception was antagonized only by β-funaltrexamine and naloxonazine. Intracerebroventricular biphalin inhibited gastrointestinal propulsion at doses 8-fold higher than those producing i.c.v. antinociception; i.c.v. morphine showed a similar antinociceptive and gastrointestinal propulsion A50. I.p. biphalin, but not i.p. morphine, showed little, if any, phys. dependence, but both biphalin and morphine produced phys. dependence when equiantinociceptive doses were infused i.c.v. These results demonstrate an unusual profile for biphalin which suggests a potentially novel mechanism which may involve, in part, the putative opioid receptor complex of phys. or functionally interacting μ and δ2 opioid receptors. Biphalin may thus represent the first in a series of such compds. which may lead to therapeutic advantages.

IT 83916-01-2, Biphalin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(analgesic action of, receptors involvement in)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

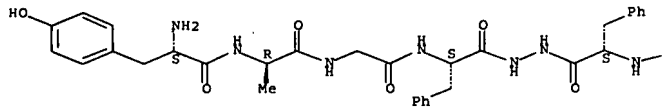
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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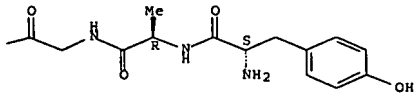


L46 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:651786 CAPLUS Full-text
DOCUMENT NUMBER: 117:251786
TITLE: Preparation of double-enkephalin (biphalin) derivatives as analgesic and antitussive agents
INVENTOR(S): Suzuki, Tsutomu; Miyao, Kohei; Chin, Shen; Imabayashi, Masayuki; Hiramori, Tameo; Nishimura, Motoo
PATENT ASSIGNEE(S): Roman Kogyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 04149195 | A | 19920522 | JP 1990-269767 | 19901008 <-- |
| PRIORITY APPLN. INFO.: | | | JP 1990-269767 | 19901008 <-- |

OTHER SOURCE(S): MARPAT 117:251786

AB [(R1)nTyr-D-Ala-Gly-(R2)mPhe-NH]2 (I; R1 = lower alkyl; R2 = lower alkyl, cyclopropylalkyl, allyl; n, m = 0,1) are prepared Thus, condensation of Z-MePhe-NHNH2 (Z = PhCH2O2C) (preparation given) with Z-MePhe-ONP (NP = p-nitrophenyl) (preparation given) in the presence of 1-hydroxybenzotriazole in CHCl3 gave 31.5% (Z-MePhe-NH)2 which was deprotected with 5N HBr in AcOH to give 92.5% (HBr.H-MePhe-NH)2. Condensation of this with BOC-MeTyr-D-Ala-Gly-OH in the presence of Et3N, DCC, and 1-hydroxybenzotriazole in DMF gave 37.7% (BOC-MeTyr-D-Ala-Gly-MePhe-NH)2 which was deprotected with 1N HCl in AcOH to give 56.2% (HCl.H-MeTyr-D-Ala-Gly-MePhe-NH)2 (II). II and I.HCl (R1 = Me, R2 = Et) showed ED50 of 0.15 and 1.85 μg/kg in inhibiting leg licking or jumping response of rats placed on a hot plate vs. 2.00 and 3.26 μg/kg for morphine and biphalin, resp.

IT 144557-92-6P 144557-93-7P 144557-94-8P
144557-95-9P 144557-96-0P 144596-67-8P
144596-68-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as analgesic and antitussive agent)





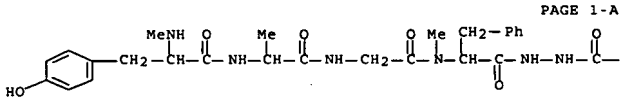
RN 144557-92-6 CAPLUS
CN L-Phenylalanine, N-methyl-N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-, 2-[N-methyl-N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-L-phenylalanyl]hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

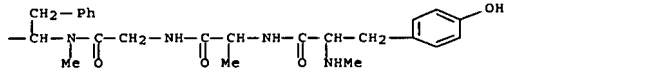
1 YAGF

PAGE 1-A



●2 HCl

PAGE 1-B



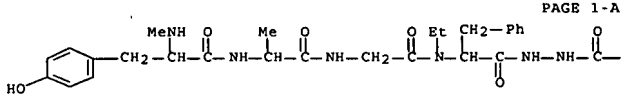
RN 144557-93-7 CAPLUS
CN L-Phenylalanine, N-ethyl-N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-, 2-[N-ethyl-N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-L-phenylalanyl]hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

PAGE 1-A



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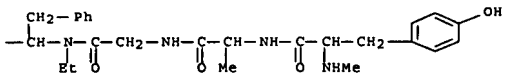
PAGE 1-B



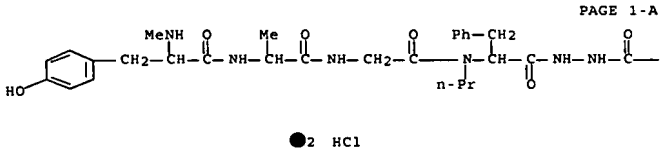
RN 144557-94-8 CAPLUS
CN L-Phenylalanine, N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-N-propyl-, 2-[N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-N-propyl-L-phenylalanyl]hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

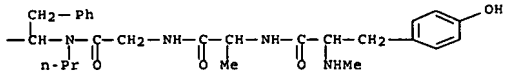
1 YAGF

PAGE 1-A



●2 HCl

PAGE 1-B



RN 144557-95-9 CAPLUS
CN L-Phenylalanine, N-(cyclopropylmethyl)-N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-, 2-[N-(cyclopropylmethyl)-N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-L-phenylalanyl]hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

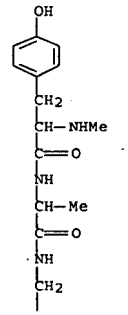
SEQ 1 YAGF

1 YAGF

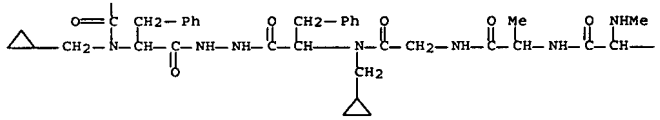




PAGE 1-A

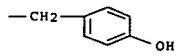


PAGE 2-A



●2 HCl

PAGE 2-B



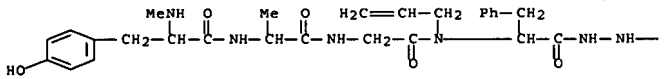
RN 144557-96-0 CAPLUS
CN L-Phenylalanine, N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-N-2-propenyl-, 2-[N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-N-2-propenyl-L-phenylalanyl]hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

PAGE 1-A



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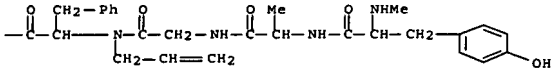
PAGE 1-B



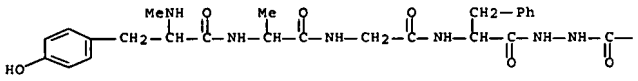
RN 144596-67-8 CAPLUS
CN L-Phenylalanine, N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-, 2-[N-[N-[N-(N-methyl-L-tyrosyl)-D-alanyl]glycyl]-L-phenylalanyl]hydrazide, dihydrochloride (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

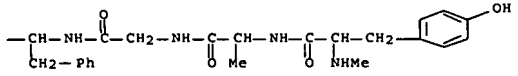
1 YAGF

PAGE 1-A



●2 HCl

PAGE 1-B



RN 144596-68-9 CAPLUS
CN L-Phenylalanine, N-methyl-N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-, 2-[N-methyl-N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-L-phenylalanyl]hydrazide,





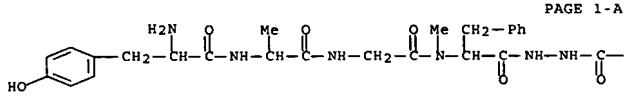
dihydrochloride (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

PAGE 1-A



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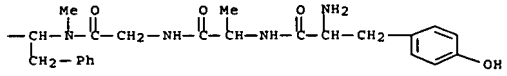
PAGE 1-B



IT 144558-01-0P 144558-07-6P 144558-13-4P
144558-20-3P 144558-27-0P 144558-28-1P
144558-29-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for analgesic and antitussive biphalin derivative)

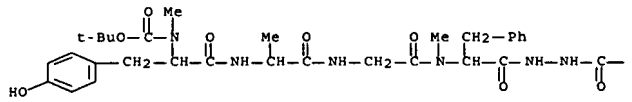
RN 144558-01-0 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-N-methyl-, 2-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-N-methyl-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

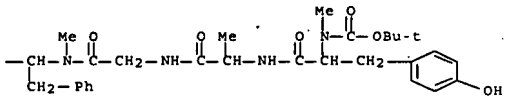
SEQ 1 YAGF

1 YAGF

PAGE 1-A



PAGE 1-B



RN 144558-07-6 CAPLUS
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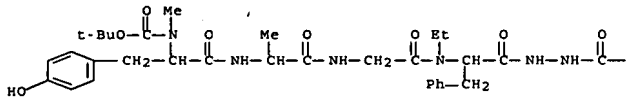
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

PAGE 1-A



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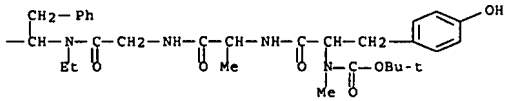


RN 144558-13-4 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-N-propyl-, 2-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-N-propyl-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

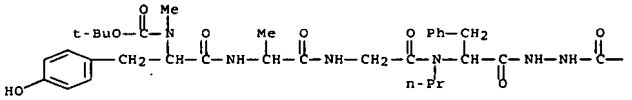
SEQ 1 YAGF

1 YAGF





PAGE 1-A



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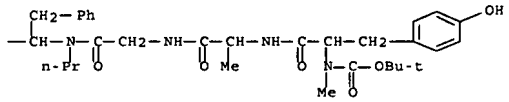

RN 144558-20-3 CAPLUS
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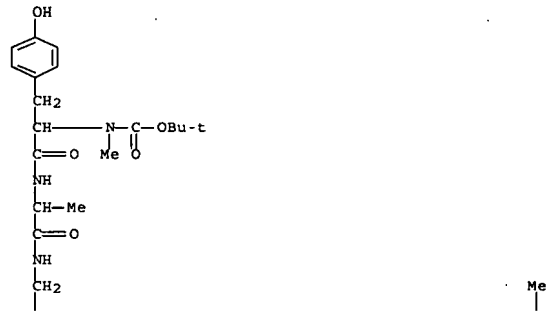
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

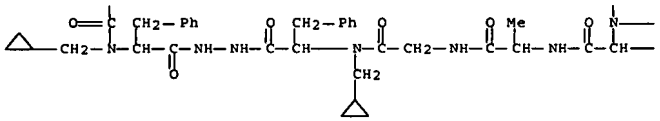
PAGE 1-A



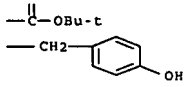
PAGE 1-B



PAGE 2-A



PAGE 2-B



RN 144558-27-0 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-N-2-propenyl-, 2-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-N-2-propenyl-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

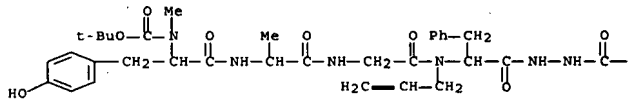
SEQ 1 YAGF

1 YAGF

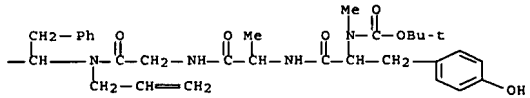




PAGE 1-A



PAGE 1-B



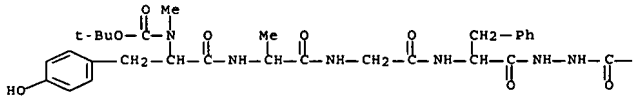
RN 144558-28-1 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-, 2-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-tyrosyl]-D-alanyl]glycyl]-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

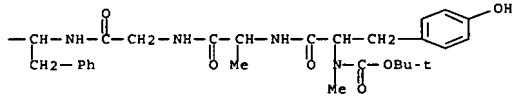
SEQ 1 YAGF

1 YAGF

PAGE 1-A



PAGE 1-B



RN 144558-29-2 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl]-D-

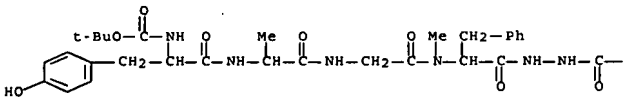
alanyl]glycyl]-N-methyl-, 2-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl]-D-alanyl]glycyl]-N-methyl-L-phenylalanyl]hydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

PAGE 1-A



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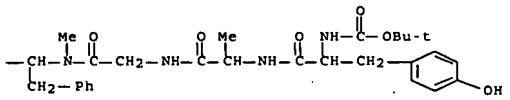


L46 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:526619 CAPLUS Full-text
DOCUMENT NUMBER: 113:126619
TITLE: Enkephalin derivative as antitussive
INVENTOR(S): Kamei, Junzo; Kasuya, Yutaka
PATENT ASSIGNEE(S): Roman Kogyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 02032028 | A | 19900201 | JP 1988-181275 | 19880719 <-- |
| JP 2700799 | B2 | 19980121 | | |

PRIORITY APPLN. INFO.: JP 1988-181275 19880719 <--

AB An antitussive contains biphalin or its pharmaceutically acceptable salts. The pharmacol. activity was demonstrated in rats.

IT 83916-01-2
RL: BIOL (Biological study)
(antitussive)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)





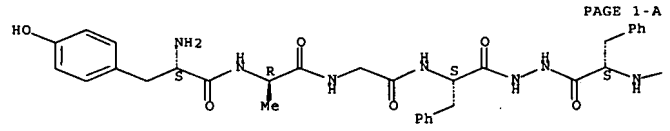
NTE multichain

SEQ 1 YAGF

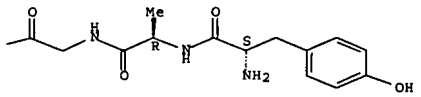
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L46 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:417905 CAPLUS Full-text
DOCUMENT NUMBER: 113:17905
TITLE: Analgesics containing enkaphalins
INVENTOR(S): Suzuki, Tsutomu
PATENT ASSIGNEE(S): Roman Kogyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 3 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 02032027 | A | 19900201 | JP 1988-181276 | 19880719 <-- |

PRIORITY APPLN. INFO.: JP 1988-181276 19880719 <--

AB Analgesics contain enkaphalins (I) or its pharmaceutically acceptable salts. I.HCl at 2 mg/kg + 24 times i.v. for 3 days showed better analgesic effect and less phys. dependency in rats than morphine.

IT 83916-01-2 127761-20-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(analgesics containing, decreased phys. dependency in relation to)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

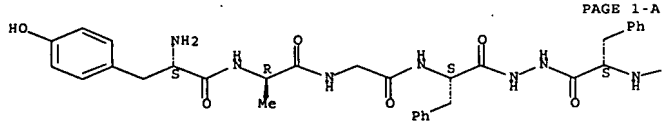
NTE multichain

SEQ 1 YAGF

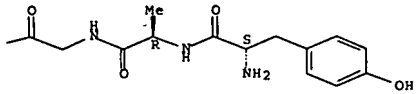
1 YAGF

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RN 127761-20-0 CAPLUS
CN L-Phenylalanine, N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-, 2-[N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-L-phenylalanyl]hydrazide, hydrochloride (9CI) (CA INDEX NAME)

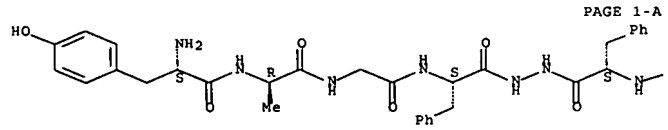
NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A

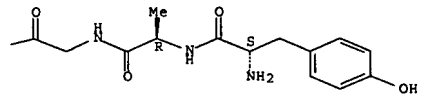


●x HCl





PAGE 1-B



L46 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:18690 CAPLUS Full-text
DOCUMENT NUMBER: 110:18690
TITLE: Effects of double-enkephalin (biphalin), an enkephalin analog, on respiration and the cough reflex in rats
AUTHOR(S): Kamei, Junzo; Kasuya, Yutaka
CORPORATE SOURCE: Sch. Pharm., Hoshi Univ., Tokyo, 142, Japan
SOURCE: Journal of Pharmacobio-Dynamics (1988), 11(9), 645-50
CODEN: JOPHDQ; ISSN: 0386-846X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacol. actions of biphalin [(HCl-Try-D-Ala-Gly-Phe-NH-)2] on nociception, respiration, and the cough reflex were compared with those of morphine in anesthetized rats. Double-enkephalin (D-Enk), injected i.p., produced analgesia at doses of 10 and 20 mg/kg in a hot-plate test. The analgesic effect of D-Enk was antagonized by pretreatment with naloxone (5 mg/kg, i.p.). D-Enk and morphine (M) produced a dose-dependent decrease in the frequency of respiration (RF) and in the tidal volume (Vt). However, the effects of D-Enk on RF and Vt were weaker than those of M. The 50% antitussive dose of D-Enk and M were 0.63 and 0.48 mg/kg, i.p., resp. The antitussive effect of D-Enk was antagonized by pretreatment with naloxone (0.4 mg/kg, i.p.). Thus, D-Enk exerted an antitussive effect similar to that of morphine, and the involvement of opiate receptors is associated with the antitussive effect of D-Enk.

IT 83916-01-2
RL: BIOL (Biological study)
(cough reflex and respiration response to)
RN 83916-01-2 CAPLUS
CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl]hydrazide (CA INDEX NAME)

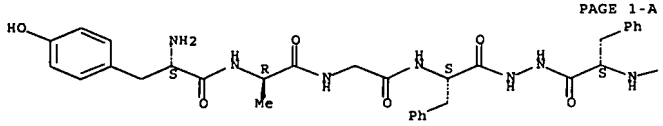
NTE multichain

SEQ 1 YAGF

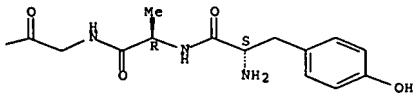
1 YAGF

Absolute stereochemistry.

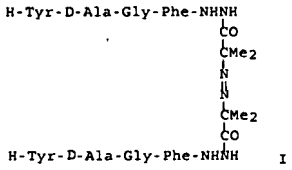
PAGE 1-A



PAGE 1-B



L46 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:132297 CAPLUS Full-text
DOCUMENT NUMBER: 108:132297
TITLE: Synthesis, and conformational and biological study of 2-D-Ala,5-des-Met-enkephalin hydrazide modified at the carboxylic end by poly-N-vinylimidazole
AUTHOR(S): Vlasov, G. P.; Krasnikova, E. N.; Kozhevnikova, N. Ya.; Illarionova, N. G.; Denisov, I.
CORPORATE SOURCE: Inst. Macromol. Compd., Leningrad, USSR
SOURCE: Biopolymers (1987), 26(9), 1489-98
CODEN: BIPMAA; ISSN: 0006-3525
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Enkephalin analog I was prepared by solution methods. N-Vinylimidazole was polymerized in the presence of I to give poly-N-vinylimidazole derivs. of I. The effects of the above modification of the above tetrapeptide on its conformational properties and biol. activity were studied.

IT 113312-53-1DP, poly(vinylimidazole) derivs.
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and conformation and analgesic activity of)





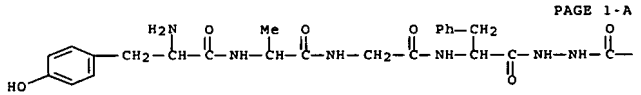
RN 113312-53-1 CAPLUS
CN L-Phenylalanine, N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-, 2,2'-[azobis(2,2-dimethyl-1-oxo-2,1-ethanediyl)]dihydrazide (9CI) (CA INDEX NAME)

NTE multichain

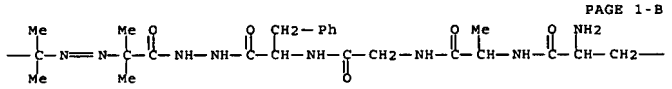
SEQ 1 YAGF

1 YAGF

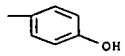
PAGE 1-A



PAGE 1-B



PAGE 1-C



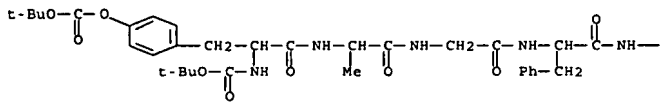
IT 113312-52-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deblocking of)
RN 113312-52-0 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N,O-bis[(1,1-dimethylethoxy)carbonyl]-L-tyrosyl]-D-alanyl]glycyl]-, 2,2'-[azobis(2,2-dimethyl-1-oxo-2,1-ethanediyl)]dihydrazide (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

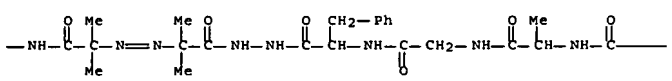
SEQ 1 YAGF

1 YAGF

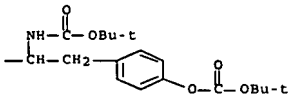
PAGE 1-A



PAGE 1-B



PAGE 1-C



IT 113312-54-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and polymerization of vinylimidazole in presence of)
RN 113312-54-2 CAPLUS
CN L-Phenylalanine, N-[N-(N-L-tyrosyl-D-alanyl)glycyl]-, 2,2'-[azobis(2,2-dimethyl-1-oxo-2,1-ethanediyl)]dihydrazide, bis(4-methylbenzenesulfonate) (salt) (9CI) (CA INDEX NAME)

NTE multichain
modified (modifications unspecified)

SEQ 1 YAGF

1 YAGF

CM 1

CRN 113312-53-1
CMF C54 H70 N14 O12

NTE multichain

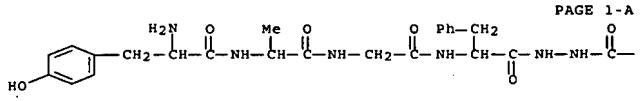
SEQ 1 YAGF

1 YAGF

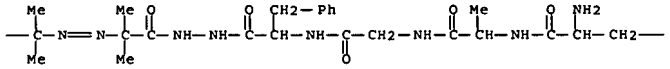




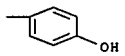
PAGE 1-A



PAGE 1-B

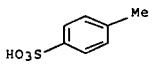


PAGE 1-C



CM 2

CRN 104-15-4
CMF C7 H8 O3 S



L46 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:546411 CAPLUS Full-text
DOCUMENT NUMBER: 105:146411
TITLE: Analgesic activity of double endorphins in vivo
AUTHOR(S): Dorociak, Anna; Misterek, Krystyna; Rewerski, Wojciech; Ciupak, Stefania
CORPORATE SOURCE: Zakl. Farmokodyn., Akad. Med., Warsaw, 00-927, Pol.
SOURCE: Acta Physiologica Polonica (1985), 35(4), 310-16
CODEN: APYPAY; ISSN: 0044-6033
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of double opiate peptides, (Tyr-D-Ala-Gly-Phe-NH-)2 (I) [83916-01-2], (Tyr-D-Ala-Phe-NH-)2 (II) [88191-63-3], and (Tyr-Pro-Phe-NH-)2 (III) [88191-66-6] on the pain threshold in rats were compared with those of D-Ala2-Met5-enkephalinamide (IV) [61090-95-7]. The analgesic activity of the peptides was decreasing in the following order: I > IV > II > III. Evidently

the glycine residue in position 3 is important for the analgesic action of the peptides.

IT 83916-01-2
RL: BIOL (Biological study)
(analgesia from, structure in relation to)

RN 83916-01-2 CAPLUS

CN L-Phenylalanine, L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (CA INDEX NAME)

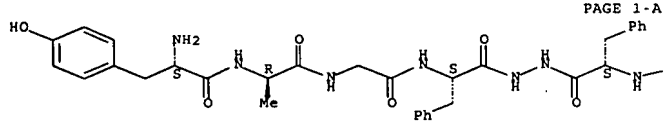
NTE multichain

SEQ 1 YAGF

1 YAGF

Absolute stereochemistry.

PAGE 1-A



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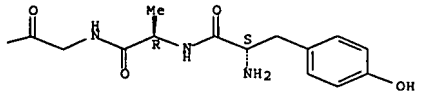





COMPOUND SEARCHED AS A STRUCTURE

=> fil reg; d stat que l6
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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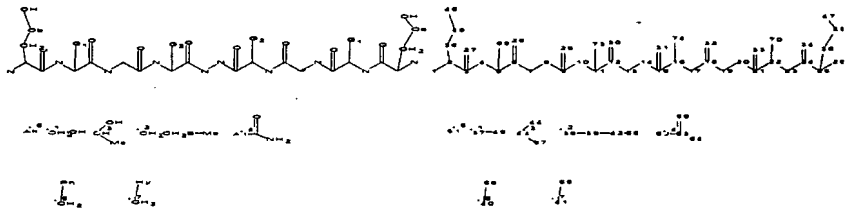
http://www.cas.org/support/stngen/stndoc/properties.html

L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

Uploading L1.str



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48 49 50 51 53 54 55 56 57 58 59 69 70 73 74
ring/chain nodes :

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24  25  26
chain bonds :
2-35  3-27  5-69  6-28  9-29  11-73  12-30  15-31  16-74  18-32  21-33  22-70  24-
34  25-36  35-48  36-49  37-45  38-39  39-42  40-58  41-59  42-56  43-44  43-57
46-48  47-49  50-53  53-54  53-55
ring/chain bonds :
1-2  2-3  3-4  4-5  5-6  6-7  7-8  8-9  9-10  10-11  11-12  12-13  13-14  14-15
15-16  16-17  17-18  18-19  19-20  20-21  21-22  22-23  23-24  24-25  25-26
exact/norm bonds :
1-2  2-3  3-4  3-27  4-5  5-6  5-69  6-7  6-28  7-8  8-9  9-10  9-29  10-11  11-12
11-73  12-13  12-30  13-14  14-15  15-16  15-31  16-17  16-74  17-18  18-19  18-32
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exact bonds :
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G1:[*1],[*2],[*3],[*4],[*5]

G2:[*6],[*7]

Connectivity :
8:2 E exact RC ring/chain  19:2 E exact RC ring/chain  50:2 E exact RC ring/chain
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Match level :
1:CLASS  2:CLASS  3:CLASS  4:CLASS  5:CLASS  6:CLASS  7:CLASS  8:CLASS  9:CLASS
10:CLASS  11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS
18:CLASS  19:CLASS  20:CLASS  21:CLASS  22:CLASS  23:CLASS  24:CLASS  25:CLASS
26:CLASS  27:CLASS  28:CLASS  29:CLASS  30:CLASS  31:CLASS  32:CLASS  33:CLASS
34:CLASS  35:CLASS  36:CLASS  37:CLASS  38:CLASS  39:CLASS  40:CLASS  41:CLASS
42:CLASS  43:CLASS  44:CLASS  45:CLASS  46:CLASS  47:CLASS  48:Atom  49:Atom
50:CLASS  51:CLASS  53:CLASS  54:CLASS  55:CLASS  56:CLASS  57:CLASS  58:CLASS
59:Atom  69:CLASS  70:CLASS  73:CLASS  74:CLASS
Generic attributes :
59:
Saturation             : Unsaturated
Number of Hetero Atoms : Exactly 1
Type of Ring System    : Polycyclic

Element Count :
Node 59: Limited
    N,N1
    C,C8


L6           43 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED    4709 ITERATIONS                          43 ANSWERS
SEARCH TIME: 00.00.01



=> s l6 not l26
L47          2 L6 NOT L26

=> fil capl; s l47
FILE 'CAPLUS' ENTERED AT 12:14:41 ON 04 DEC 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 4 Dec 2007  VOL 147 ISS 24
FILE LAST UPDATED: 3 Dec 2007  (20071203/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L48          1 L47

=> d ibib abs hitstr l48; fil hom

L48  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        1998:169052  CAPLUS  Full-text
DOCUMENT NUMBER:         128:290334
TITLE:                   [125I-Tyr1]biphalin binding to opioid receptors of rat
                         brain and NG108-15 cell membranes
AUTHOR(S):               Slaninova, Jirina; Appleyard, Suzanne M.; Misicka,
                         Aleksandra; Lipkowski, Andrzej W.; Knapp, Richard J.;
                         Weber, Steven J.; Davis, Thomas P.; Yamamura, Henry
                         I.; Hruby, Victor J.
CORPORATE SOURCE:        Department of Pharmacology, University of Arizona,
                         Tucson, AZ, 85721, USA
SOURCE:                  Life Sciences (1998), 62(14), PL199-PL204
                         CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER:               Elsevier Science Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB    Mono iodinated analogs of biphalin [(Tyr-D-Ala-Gly-Phe-NH-)2], both
      nonradioactive [I-Tyr1]biphalin and radioactive [125I-Tyr1]biphalin have been
      synthesized.  The radioligand binding profiles of these compds. for two types
      of tissues, rat brain membranes, and NG108-15 cell membranes were identical to
      the parent biphalin.  This is addnl. evidence for the hypothesis that biphalin
      behaves like a monomeric ligand and that only one intact tyrosine is necessary
      for high biol. activity.  The second tyrosine could be used for successful
      radioiodination which may greatly simplify biochem. and pharmacol. studies of
      biphalin.  The results of receptor binding studies show that the binding of
      both biphalin and [I-Tyr1]biphalin to the δ and μ opioid receptors are not
      independent.  [125I-Tyr1]Biphalin binds to δ receptors as shown in NG108-15
      cell membranes.  Nevertheless, [125I]biphalin binding to δ receptors in rat
      brain membranes was hardly evident and μ receptor binding predominated or at
      least was much more readily detectable in this preparation
IT    206054-29-7P
      RL: BAC (Biological activity or effector, except adverse); BSU (Biological
```

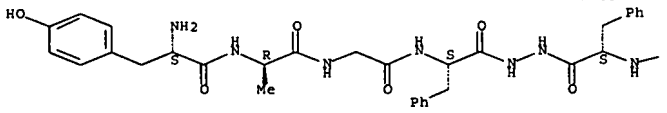
study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mono iodinated biphalin analogs binding to opioid receptors of rat brain and NG108-15 cell membranes)

RN 206054-29-7 CAPLUS

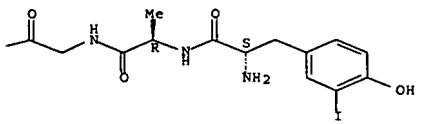
CN L-Phenylalanine, 3-iodo-L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT 206054-30-0P

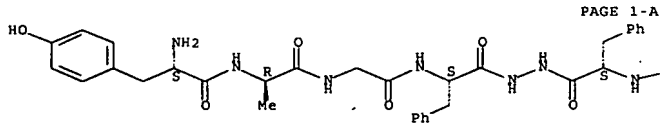
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mono iodinated biphalin analogs binding to opioid receptors of rat brain and NG108-15 cell membranes)

RN 206054-30-0 CAPLUS

CN L-Phenylalanine, 3-(iodo-125I)-L-tyrosyl-D-alanylglycyl-, 2-(L-tyrosyl-D-alanylglycyl-L-phenylalanyl)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

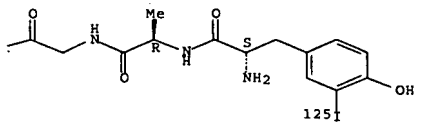
PAGE 1-A







PAGE 1-B



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

FILE 'HOME' ENTERED AT 12:15:00 ON 04 DEC 2007

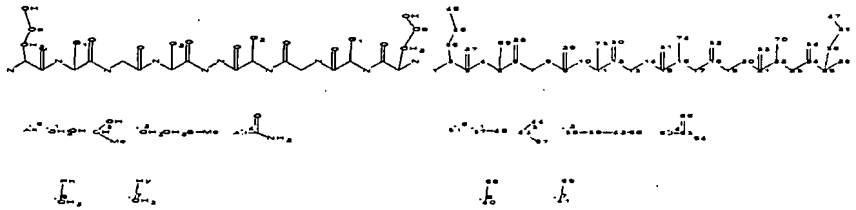
SEARCH HISTORY

=> d stat que 16; d his nofile
L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

Uploading L1.str



chain nodes :
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47
48 49 50 51 53 54 55 56 57 58 59 69 70 73 74
ring/chain nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
24 25 26
chain bonds :
2-35 3-27 5-69 6-28 9-29 11-73 12-30 15-31 16-74 18-32 21-33 22-70 24-
34 25-36 35-48 36-49 37-45 38-39 39-42 40-58 41-59 42-56 43-44 43-57
46-48 47-49 50-53 53-54 53-55
ring/chain bonds :
1-2 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 12-13 13-14 14-15
15-16 16-17 17-18 18-19 19-20 20-21 21-22 22-23 23-24 24-25 25-26
exact/norm bonds :
1-2 2-3 3-4 3-27 4-5 5-6 5-69 6-7 6-28 7-8 8-9 9-10 9-29 10-11 11-12
11-73 12-13 12-30 13-14 14-15 15-16 15-31 16-17 16-74 17-18 18-19 18-32
19-20 20-21 21-22 21-33 22-23 22-70 23-24 24-25 24-34 25-26 41-59 43-44
50-53 53-54 53-55
exact bonds :
2-35 25-36 35-48 36-49 37-45 38-39 39-42 40-58 42-56 43-57 46-48 47-49

G1:[*1],[*2],[*3],[*4],[*5]

G2:[*6],[*7]

Connectivity :
8:2 E exact RC ring/chain 19:2 E exact RC ring/chain 50:2 E exact RC ring/chain
51:1 E exact RC ring/chain
Match level :





1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS
18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS
26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS
34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS 40:CLASS 41:CLASS
42:CLASS 43:CLASS 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:Atom 49:Atom
50:CLASS 51:CLASS 53:CLASS 54:CLASS 55:CLASS 56:CLASS 57:CLASS 58:CLASS
59:Atom 69:CLASS 70:CLASS 73:CLASS 74:CLASS
Generic attributes :
59:
Saturation : Unsaturated
Number of Hetero Atoms : Exactly 1
Type of Ring System : Polycyclic

Element Count :
Node 59: Limited
N,N1
C,C8

L6 43 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 4709 ITERATIONS 43 ANSWERS
SEARCH TIME: 00.00.01

(FILE 'HOME' ENTERED AT 10:44:41 ON 04 DEC 2007)

FILE 'REGISTRY' ENTERED AT 10:44:54 ON 04 DEC 2007
L1 STRUCTURE UPLOADED
L2 0 SEA SSS SAM L1

FILE 'CAPLUS' ENTERED AT 10:45:45 ON 04 DEC 2007
E US2005-524343/APPS
E US2006-524343/APPS
L3 1 SEA ABB=ON US2006-524343/AP
D SCAN
SEL RN

FILE 'REGISTRY' ENTERED AT 11:09:58 ON 04 DEC 2007
L4 13 SEA ABB=ON (659732-80-6/BI OR 659732-81-7/BI OR 659732-82-8/BI
OR 659732-83-9/BI OR 659732-84-0/BI OR 659732-85-1/BI OR
659732-86-2/BI OR 659732-87-3/BI OR 659732-88-4/BI OR 659732-89
-5/BI OR 659732-90-8/BI OR 83916-01-2/BI OR 88191-65-5/BI)
D SCAN
D SQIDE
E COVALENT/NTE
D STAT QUE L2
L5 4709 SEA SSS FUL L1 EXTEND
L6 43 SEA SSS FUL L1
SAVE TEMP L6 HA343FULL/A
L7 66323 SEA ABB=ON Y[SMLQATN]G[FW]/SQSP
L8 20680 SEA ABB=ON MULTICHAIN/NTE

```
L9          283 SEA ABB=ON  L7 AND L8
L10       14340 SEA ABB=ON  COVALENT/NTE
L11         236 SEA ABB=ON  L9 AND L10
L12         145 SEA ABB=ON  L11 AND 8/SQL
L13      734823 SEA ABB=ON  HYDRAZIDE
L14          90 SEA ABB=ON  L12 AND L13
                SAVE TEMP L14 HA343SEQ/A
L15           2 SEA ABB=ON  L6 NOT L14
L16          49 SEA ABB=ON  L14 NOT L6
                D SCAN L15
L17       66323 SEA ABB=ON  L7(S)L7

     FILE 'LREGISTRY' ENTERED AT 11:22:46 ON 04 DEC 2007
L18          29 SEA ABB=ON  Y[SMLQATN]G[FW]/SQSP
L19          29 SEA ABB=ON  MULTICHAIN/NTE
L20           0 SEA ABB=ON  L18 AND L19
                D SCAN L19
L21           2 SEA ABB=ON  ACTINOMYCIN D
L22           2 SEA ABB=ON  L19 AND L21
                D SQIDE
                D SQIDE 2
L23           8 SEA ABB=ON  TVP.V/SQSP
L24           8 SEA ABB=ON  TVP.V/SQSP(L)TVP.V/SQSP
                D SCAN L24
L25           3 SEA ABB=ON  L19 AND L23

     FILE 'REGISTRY' ENTERED AT 11:28:08 ON 04 DEC 2007
                D SCAN L16

     FILE 'STNGUIDE' ENTERED AT 11:29:09 ON 04 DEC 2007

     FILE 'REGISTRY' ENTERED AT 11:41:30 ON 04 DEC 2007
L26          57 SEA ABB=ON  L14 NOT (NORLEU? OR TRICYCLO? OR LYS?)
L27          16 SEA ABB=ON  L26 NOT L6
                D SCAN
L28          33 SEA ABB=ON  L16 NOT L27

     FILE 'CAPLUS' ENTERED AT 11:44:07 ON 04 DEC 2007
L29          62 SEA ABB=ON  L6
L30          11 SEA ABB=ON  L27
L31          10 SEA ABB=ON  L29 AND L30
L32         199 SEA ABB=ON  LIPKOWSKI A?/AU
L33         895 SEA ABB=ON  CARR D?/AU
L34          11 SEA ABB=ON  BONNEY I?/AU
L35         127 SEA ABB=ON  KOSSON D?/AU
L36           4 SEA ABB=ON  MISJECKA KESIK A?/AU OR MISJECKA A?/AU OR KESIK
                A?/AU
                D BIB L3
L37           2 SEA ABB=ON  MISIECKA-KESIK A?/AU OR MISIECKA A?/AU
L38          30 SEA ABB=ON  (L3 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37) AND
                (L29 OR L30)
L39          54 SEA ABB=ON  (L29 OR L30) AND (PY<2004 OR AY<2004 OR PRY<2004)

     FILE 'CAPLUS' ENTERED AT 11:47:54 ON 04 DEC 2007
                D QUE NOS L38
L40          30 SEA ABB=ON  (L3 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37) AND
                L29
L41           7 SEA ABB=ON  (L3 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37) AND
                L30
```





```
     FILE 'CAPLUS' ENTERED AT 11:49:27 ON 04 DEC 2007
                D QUE NOS L41
                D IBIB ABS HITSEQ L41 1-7
                D QUE NOS L40
L42          23 SEA ABB=ON  L40 NOT L41
                D IBIB ABS HITSTR L42 1-23

     FILE 'REGISTRY' ENTERED AT 11:50:54 ON 04 DEC 2007
                D STAT QUE L6

     FILE 'STNGUIDE' ENTERED AT 11:59:27 ON 04 DEC 2007

     FILE 'REGISTRY' ENTERED AT 12:11:53 ON 04 DEC 2007
L43          41 SEA ABB=ON  L26 AND L6
                D QUE L26

     FILE 'CAPLUS' ENTERED AT 12:13:05 ON 04 DEC 2007
L44          63 SEA ABB=ON  L26
L45          33 SEA ABB=ON  L44 NOT (L41 OR L42)
L46          25 SEA ABB=ON  L45 AND (PY<2004 OR AY<2004 OR PRY<2004)
                D IBIB ABS HITSEQ L46 1-25

     FILE 'REGISTRY' ENTERED AT 12:14:27 ON 04 DEC 2007
                D STAT QUE L6
L47           2 SEA ABB=ON  L6 NOT L26

     FILE 'CAPLUS' ENTERED AT 12:14:41 ON 04 DEC 2007
L48           1 SEA ABB=ON  L47
                D IBIB ABS HITSTR L48

     FILE 'HOME' ENTERED AT 12:15:00 ON 04 DEC 2007
                D STAT QUE L6

=>
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